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## LOW BACK PAIN

### CORRELATION OF SOME OF THE SIGNS AND SYMPTOMS


JOSEPH A. FREIBERG, M.D.

CINCINNATI


During the past five years especially, great strides have been made toward a clearer understanding of the protean causes of low back pain. With this broader knowledge, contributed to by many orthopedic surgeons and neurosurgeons, the accurate diagnosis of low back pain has become most complicated. It has not been many years since the differential diagnosis rested only between a lumbosacral or a sacro-iliac lesion as the cause of both low back pain and so-called sciatica. Many of those who studied the problem from day to day and year to year were of the impression that they understood the subject completely, only to run up against a blank wall of misunderstanding at too frequent intervals. Many orthopedic surgeons believed that the problem was simple and that it was merely a question of differentiation between lesions in the two regions, lumbosacral area versus sacro-iliac joints. The fact that there were many signs and symptoms common to the two lesions was known but not fully appreciated. The fact that the lumbosacral protagonists cured a large proportion of their patients, as did also the sacro-iliac exponents, was a constant source of forensic debate. Now one is able to appreciate, to a certain extent, why neither school of thought was completely convincing: because there was actually a third lesion, the herniated or protruded intervertebral disk, then unrecognized in its frequent role as a cause of low back pain and sciatica. Today we see this herniated disk lesion invested with tremendous responsibilities—possibly too great responsibilities. Though this pathologic lesion is a definite, proved clinical entity and its recognition and removal have cured many patients, one must not become overzealous and believe that this lesion alone is responsible for the majority of cases of low back pain, with or without sciatic pain.

At the same time that the herniated disk syndrome has become better known, so also have the intricate and less obvious muscular and fascial lesions about the lower part of the back, pelvis and thigh yielded to clinical and scientific study. Physicians are faced now with many more functional and organic causes for the acute and the chronic low back pain and with a much greater differential diagnostic problem. Likewise, as the surgical procedures developed to attack these several newer lesions are accompanied by relatively little danger to the general health and life of the patient, surgery has assumed an even more common means of treating the many who suffer pain in the back. The proponents of the several newer surgical procedures for the relief of such pain have sounded many warnings and admonitions regarding the too free use of these operations, but what orthopedic surgeon has not seen patients with the back pain or sciatica still present after one, two or three operations. The last operation is usually successful, but could not the previous one or two have been avoided? Again, have conservative means, such as postural training, traction, manipulation, physical therapy and braces, been used intelligently before surgical attack has been carried out? In many cases early surgical treatment is to the great advantage of the patient, but in other series careful study of the individual patient will show that nonsurgical therapy alone is indicated in from 80 to 90 per cent of the cases.

In this discussion the infectious lesions capable of causing low back pain have been excluded because, in general, they are more readily recognized, and when recognized the therapy is well indicated. Suffice it to say that an active infectious lesion is treated conservatively and that a painful or unstable joint due to a preexisting infectious process must be immobilized either by muscular or mechanical support or by operative fixation.

### DIAGNOSIS

The real diagnostic problem in low back pain, with or without sciatica, is to differentiate between the primary and secondary causes for the pain and to evaluate their relative significance with regard to therapy. There are several conditions in which treatment of the secondary lesion alone relieves the pain temporarily, and even permanently, but when this plan of therapy is relied on it must be used knowingly. In the lower part of the back there are numerous true joints: those between the lumbar articular processes and the sacro-iliac joints. Traumatic or infectious processes involving one or more of these joints is accompanied by an involuntary muscle splinting or muscle spasm, response similar to that associated with lesions in other joints in the body. This muscle spasm associated with low back lesions may involve one or more muscle groups of the spine, pelvis or thigh. Dissimilar lesions may be and are associated with similar types of muscle spasm responses. Therefore the clinical picture of the so-called sciatic scoliosis, with limitation of normal mobility of the lumbosacral joints and restriction of the straight leg-raising test, cannot be indicative of any one lesion. Likewise, as the muscle spasm, per se, may be painful or may cause secondary painful areas, it is frequently difficult to differentiate between the primary lesion causing the muscle spasm and the secondary lesion, which is sometimes the true cause of the pain. It is this situation, peculiar to the low back lesions, which has caused the


From the Department of Orthopedic Surgery, University of Cincinnati.


Read before the Section on Orthopedic Surgery at the Ninetieth Annual Session of the American Medical Association, St. Louis, May 17, 1939.

confusion of diagnoses and therapeutic procedures. Add to this picture the rather frequent anomalies of structural development of the osseous tissues in the lumbosacral area, and the maze is complete.

The primary lesion associated with low back pain may be a true joint lesion, synovitis, a ligamentous trauma, periostitis at the site of muscle origin or insertion, myositis, fasciitis or a lesion of the intervertebral disk. The etiologic factor initiating the syndrome of back pain, with or without sciatica, may be a trauma disrupting the normal function of a joint, a ligamentous or periosteal tear associated with primary localized hemorrhage and secondary fibrous or scar tissue formation. It may be a gradual fascial or muscular contracture dependent primarily on faulty posture. In this last instance the faulty posture may be due to an osseous anomaly associated either with hypermobility and instability of the lumbosacral or fourth and fifth lumbar articulations or muscle imbalance dependent on some other cause, such as pregnancy with persisting relaxation of the abdominal muscles. The primary lesion in many cases is similar to lesions occurring commonly about other joints of the body but obscured because of the intricate mechanism involved in the lower part of the back. Furthermore, this joint or ligamentous lesion initiates a series of muscle responses which may be common to all of the different primary lesions.

Obviously, before an attempt is made to treat a syndrome involving low back pain the lesion must be identified. The history of the mode of onset is especially important. Was there a trauma and, if so, what was its nature? Have there been previous similar attacks, were they induced in a similar manner, and was leg pain or sciatica invariably present? Have the initial symptoms persisted, or did they disappear as new symptoms developed? In other words, in many cases the history will clearly bring out the fact that there was a single site of pain and tenderness, subsequently masked by the gradual development of secondary symptoms. The story of something slipping or snapping as a primary symptom should not be passed over lightly, as this sign usually indicates a ligamentous or periosteal tear which may well be the lesion to be treated. Postural strains, such as accompany automobile driving and faulty posture at a desk, frequently initiate a muscle imbalance causing an anomalous lumbosacral structure to become symptom producing. Equally important in the history is the fact that certain body positions or attitudes relieve the pain. Finally, the detailed history in the case of both acute and chronic backaches is just as important as in other bodily ailments.

On physical examination, the signs and symptoms associated with low backache may be numerous or few, depending on the individual case. The acute low back pain with or without sciatic pain should be approached in a manner entirely different from that suited to the chronic case. Many of the acute cases of recent onset represent ligamentous, periosteal or muscular tears with associated local bleeding. An extensive physical examination accompanied by forceful testing of the range of mobility of the various joints is definitely contraindicated, as it is in the case of acute ankle or knee lesions. Manipulation under these circumstances will tend to aggravate the lesion and increase the degree of damage, although an existing painful muscle spasm may be temporarily relieved. Observation and palpation will elicit the location of the areas of tenderness and injury. Acute ligamentous, capsular and muscular lesions elsewhere in the body are treated by immobilization and the control of local bleeding. Therefore, in similar lesions about the lower back region immobilization by adhesive strapping and bed rest, accompanied by cold compresses or ice bags, is similarly indicated for at least forty-eight hours. These soft tissue lesions require from seven to twenty-one days to heal; therefore supportive therapy should be pursued for this period. It is the failure to recognize the nature of these initial lesions which contributes toward many of the recurrences of symptoms and toward many of the secondary persisting ligamentous, fascial and muscular lesions seen in the chronic cases of low back pain. Inadequately treated ruptures of the internal lateral ligament of the knee joint result in an instability of the knee joint associated with recurrent episodes of pain, synovitis and muscular imbalance. Ligamentous tears healed by relatively wide bridges of cicatricial tissue result in elongated or contractured ligaments with a relative loss of elasticity. Untreated periosteal tears are followed by areas of organized subperiosteal hematomas and fibrous tissue infiltration. Similar sequelae develop in muscle lesions. The sites of these soft tissue lesions about the lower part of the back are fairly constant, as determined by areas of pain or, more reliably, by point tenderness on pressure.

The more severe low back injuries may be accompanied by lesser fractures involving articular processes, laminas or pedicles. The prompt recognition of a fracture involving the arcus of a vertebra and its subsequent immobilization will prevent many chronic complaints involving the lower part of the back. These fractures, although often isolated and small, are true fractures not only capable of producing symptoms but requiring from eight to ten weeks to heal. Nonunited, these lesions may offer sufficient local instability to be the basis of recurrent or constant pain.

The exact mechanism and degree of trauma preceding ruptures of the annulus fibrosus and consequent posterior protrusions of the intervertebral disks has not been definitely determined. Likewise, the less frequent lesions of the ligamentum flavum followed by hypertrophy or cicatricial thickening of the ligament are not clearly understood. That these lesions do occur and that they may be associated independently with constant or recurring attacks of low back pain with or without sciatic pain must be accepted. However, that these lesions occur and that in many cases reported by many authors complete recovery has followed laminectomy does not indicate that in all instances recovery or relief from symptoms depends solely on removal of the lesions. The functional mechanism of the lower part of the back is intricate and varies extensively with the functional demands placed on it; hence it is highly probable that more than one factor is responsible for the production of pain or dysfunction in many cases. Likewise, the elimination of one of two or more abnormal conditions in a given case may result in complete relief from symptoms and clinical recovery. From the very nature of the lesions at operation and the history of no recent injury, a protruded disk and a recent low back pain cannot always be correlated. Previous episodes of low back pain in a patient have been relieved by conservative therapy, but in a later, possibly more severe, attack a protruded disk has been discovered and removed. Was this disk the causative factor in the previous similar attack of back pain? An analogous situation may arise in the case of congenital bilateral pedicle defects of the fifth lumbar vertebra, entirely symptomless for twenty-five or more years, which are discovered associated with an attack of

low back pain with or without sciatic pain. The instability of the lumbosacral joint in this instance may be, and often is, a predisposing factor in the clinical picture; nevertheless, a certain number of these patients are cured or relieved by nonoperative therapy or by lesser operative procedures not actually involving the pedicle defects.

Some authors have reported rather large series of cases of sciatic pain, with and without low backache, entirely relieved by epidural injections, neurolysis of the sciatic nerve or injection of fluids into the sheath of the sciatic nerve. Obviously, without regard to the foregoing discussion it may be assumed that many conditions about the lower part of the back are capable of causing painful manifestations and that because of the intricate mechanism of this region no one type of lesion can be accepted as the chief etiologic factor. From one large orthopedic center the report has been made that from 80 to 90 per cent of the cases of low back pain are relieved by conservative measures. Possibly this estimate is somewhat high, but nevertheless there is too great a discrepancy between this percentage of nonsurgical cases and the figures from many smaller orthopedic centers.

## SIGNS AND SYMPTOMS

Obviously, not all of the signs and symptoms associated with low back pain can be discussed in this paper. The following features, frequently encountered, are the bases for varied clinical conclusions:

The history of acute aggravation of pain in the lower part of the back, buttock or sciatic nerve area accompanying sneezing or coughing is often attributed to an increased intraspinal fluid pressure and is consequently considered an indication of a protruded disk or of other mechanical pressure on the nerve root. On the other hand, sneezing and coughing are closely linked with spasmodic contracture of the abdominal and back muscles. Lesions of the fasciae, muscles or joints may therefore be equally affected momentarily. Especially is this true of periosteal lesions.

So-called sciatic scoliosis with flattening or convexity of the lumbar spine may accompany any acute or subacute lesions of the lower part of the back and in itself is indicative only of an irritative lesion of the neuromuscular mechanism of this region.

Relief from pain and disappearance of muscle spasm on lying down generally imply that a postural or abnormal mchanical strain has been removed from a lumbosacral or sacro-iliac joint. Intraspinal lesions, protruded disks and hypertrophied ligamenta flava usually, although not constantly, are unaffected by changing of position such as lying down or sitting.

In the presence of muscle spasm or contracture of the gluteus maximus or hamstring muscles or both, limitation of forward bending in the standing position as compared with the sitting position has relatively little significance, as in standing the affected muscles are put on increased tension and in sitting they are relieved of this tension. In the absence of muscle spasm or contracture of these muscles, however, this test aids considerably in differentiating between lumbar and sacro-iliac or fascial lesions.

Limitation of passive lumbar flexion in the supine position signifies a lumbar or lumbosacral articular lesion.

The straight leg-raising or Lasègue test when definitely positive may be interpreted in several ways: Limitation of hip flexion with the knee extended may be due to spasm of the gluteus maximus and hamstring muscles caused by lesions of these muscles or their periosteal origins, lesions of the sciatic nerve or its nerve roots, or articular lesions of the sacro-iliac or lumbosacral joints accompanied by muscle spasm. On the other hand, pain induced on one side only, regardless of which leg is tested, usually centers attention on the sacro-iliac joint of the painful side.

The Ober test for contractured thigh fascia may be positive as the result of muscle spasm involving the tensor fasciae femoris and gluteal muscles. When this test causes a localized pain, a periosteal lesion should be suspected. When the Ober test is positive during an interim between attacks of back pain it is really indicative of contracture of the fascia lata or of the iliotibial band.

The Ely, or prone knee flexion, test is one of the most valuable maneuvers to demonstrate the existence of thigh fascial contractures but not of a lumbosacral lesion, as originally described. In the first place, because of the position of the patient, spasms of the glutei and hamstrings play practically no role. If on passive flexion of the lower leg on the thigh the buttocks arch away from the table and at the same time the leg abducts at the hip joint, a true contracture of the anterior and lateral thigh fascia is demonstrated.

In the supine position with the knee extended, internal rotation of the leg followed by slight flexion of the hip and adduction of the leg may cause localized pain in the buttock. When associated with pain or pressure over the pyriformis muscle, one of two lesions is indicated: either a lesion of the pyriformis muscle or a lesion of the sciatic nerve or its sheath in the region of the pyriformis muscle.

Again in the supine position, on passive twisting or rotation of the pelvis by forcing the flexed hip and knee of one side across the body while fixing the ipsilateral shoulder, limitation of motion on one side associated with pain suggests an articular or capsular lesion of the lumbosacral or sacro-iliac joint, depending on the site of the pain. Relief from symptoms following this manipulative test is especially dramatic in some instances.

Probably the most valuable of all the tests in determining the exact site of periosteal, ligamentous or joint lesions is the localization of one or more areas of definite tenderness on palpation when the patient is lying comfortably on a firm table. Unless a careful routine is carried out, the area of maximum tenderness may be missed. The most frequent points of tenderness may be found at the following sites:

1. The supraspinous ligament between the spinous processes.
2. The periosteal attachment of the erector spinae muscles to the dorsum of the sacrum.
3. The gluteus maximus and medius origins along the iliac tuberosities and crests.
4. The pyriformis muscle, an area midway between the greater trochanter and the posterior-superior iliac spine.
5. The iliotibial tract or fascia lata over the greater trochanter and between the greater trochanter and the iliac crest.
6. The sacro-iliac notch or the posterior-inferior sacro-iliac ligaments.
7. The lumbar zygapophysial joints, about 1 inch lateral to the spinous processes.

If a single site of definite tenderness is found on palpation and the lesion is not of recent origin, the injection of a few cubic centimeters of 1 per cent procaine hydrochloride may relieve the pain temporarily

or, less frequently, permanently. This relief of pain on injection of procaine hydrochloride usually demonstrates the fact that the lesion involves periosteal or ligamentous tissues previously the seat of a trauma or inflammatory process. If the injection is in the vicinity of a nerve such as the superior or inferior gluteal it may be argued that the pain stimulus is interrupted by temporary nerve block, but this explanation is not entirely satisfactory.

In this discussion of low back pain two important types of observation are not included, namely the complete neurologic and x-ray studies. Obviously, these examinations must be included. Suffice it to say that in both the spinal studies must be correlated with the other clinical data. A diminished or absent achilles tendon reflex does not always signify the existence of a protruded intervertebral disk, but this is often the case. Subjective numbness or sensation of coldness of the leg in the absence of disturbance of sensation does not indicate an essential sciatic nerve involvement. A neurologic examination will exclude central nervous system degenerative lesions or peripheral neuritis. When the general observations suggest an intraspinal lesion, lumbar puncture studies and, if indicated, visualization studies with iodized oil should be made. The x-ray examination must also be interpreted in the light of the purely clinical features, as some anomalous osseous lesions are the cause of low backache while others are proved to be merely coincidental.

The scope of this paper does not include a discussion of therapy. If an exact diagnosis can be made, the choice of treatment is usually obvious, and a plan of preliminary conservative therapy is suggested. The fasciotomy of Ober, the periosteal stripping of Heyman, the myotomy of the pyriformis, laminectomy and fusion operations are all excellent procedures on the condition that they are carried out in carefully studied and selected cases. Contractured or permanently shortened fasciae and muscles should be stretched or cut, but fasciae and muscles under increased tension due to muscle spasm should be treated conservatively.

## CONCLUSION

Any disturbance of the mechanical function of the lower part of the back may initiate somewhat similar combinations of signs and symptoms. Ligamentous, periosteal, muscular and fascial lesions may be identified by physical examination. Restriction of motion and tenderness to palpation remain as the most significant physical features. Initial conservative, nonoperative therapy serves a twofold purpose, as a valuable diagnostic aid and as a method of curing a large number of the patients.

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## ABSTRACT OF DISCUSSION

DR. PHILIP LEWIN, Chicago: I should like to emphasize conservatism, which can easily be changed when new facts are presented. We are in a state of evolution analogous to that in which we were concerning fracture of the neck of the femur a few years ago. I should like to place before you the analogy of what I term a double U, that is one U superimposed on an inverted U, which will help to visualize some aspects of the problem. The upper U consists chiefly of the erector spinae, the intervertebral disks and ligamentum flavum lesions, the lower U, chiefly the tensor fasciae latae, and lumbosacral and sacro-iliac joint, the periformis and the coccygeus muscle. Each human leg is a fork of the theoretical U. The three points indicated are the lumbosacral and the sacro-iliac joints. The lower U is composed of the tensor fasciae latae, the sacro-iliacs, the lumbosacral joint, and the piriformis and the coccygeus muscles. When those are superimposed, one has the double U analogy. Any procedure that breaks the circuit may give, in certain selected cases, complete or partial relief. These procedures are chiefly injections, liberations, fusions and relief from pressures, such as following the operation for protrusion of the intervertebral disk and hypertrophied ligamentum flavum. One of the oldest complaints and observations with regard to backache is pain or stiffness or both on resuming activity after a period of rest. One need only to watch elderly persons arise from bridge or see a group of people get out of a bus after a long ride and observe the stiffness which appears on resuming activity. I have given it the name "postinertial dyskinesia." I should like to ask the facetious question Where do the intervertebral disks hide between attacks? Chamberlain and others have offered some plausible answers to this question. I should like to suggest the general use of the term "spondylogram" or "spinagram," like the cardiogram. I have found at operation in several cases fusion of the ligamentum flavum and the dura, which I call "ligamentothecosis" or adhesive ligamentothecitis. I believe that this lesion is definitely a trauma which may produce hemorrhage, some scarring, some more trauma, adhesions and, when the patient bends, especially forward or backward, there is a pull on the sheath and pressure on the nerve. I believe in some cases that produces pain.

DR. G. C. BATTALORA, New Orleans: There are probably no other diagnostic problems more complex than low back disorders. The difficulty is not lessened by the fact that several different conditions can give rise to a similar picture. I am going to dwell mainly on the so-called low back syndrome in which there are backache, sciatica, list of the spine to one side or the other, and positive leg signs, with absence of ankle jerks. Certain neurosurgeons rely exclusively on these manifestations in making a diagnosis of a disk lesion. The frequency with which one sees disk protrusions has struck me forcibly, in observing certain dissecting room preparations. I know well that the incidence of these protrusions does not parallel the incidence of disabling symptoms that certain patients complain of. If a patient has these symptoms and signs, with the ankle jerk absent, this absence of the ankle jerk may be due to pressure on the fourth or fifth lumbar nerve roots, either in the intraspinal spaces or perhaps outside, because of spasm in certain muscles. If one treats these cases conservatively, relieving the irritative lesions on the nerves, one can get a reestablishment of the reflexes; therefore, before making a diagnosis of a disk lesion one should exclude all other orthopedic problems.

DR. EARL D. MCBRIDE, Oklahoma City: A sign which I term the "cocked knee sign" has been puzzling to me with regard to its mechanics. It seems to be a characteristic sign in certain cases of muscle spasm associated with sciatic nerve involvement. The patient can sit erect when the knee on one side is flexed, but when both knees are flattened straight out on the table the patient has to lean backward and cannot bend forward. One would naturally feel that this is muscle spasm related to the hamstrings and gluteus muscles, but on experimenting by injecting procaine hydrochloride I have become more puzzled as to the exact mechanics.

DR. JOSEPH A. FREIBERG, Cincinnati: In this paper I made practically no mention of the piriformis operative procedure, which was first described by Dr. Albert Freiberg, of Cincinnati. The reason for this is that I have felt on further observation that the majority of the sciaticas which are dependent primarily on spasm of the piriformis muscle respond to conservative therapy. I have probably done fewer piriformis myotomies than many of the larger clinics. Regarding the diminution or absence of ankle jerk in many of these low back cases, it is my opinion that all of them cannot be explained. It is a sign of a lower motor neuron lesion, and certainly all orthopedic surgeons have seen many diminished or absent ankle jerks return to normal following conservative therapy. Whether this means, as the neurosurgeons will usually say, that a herniated or protruded disk fragment has returned to its former place of residence, I do not know, but I believe that some of them may be accounted for on the basis of a severe piriformis spasm which has responded to conservative treatment.

# THE INCIDENCE OF HEMORRHAGE OCCURRING WITH PERFORATION IN PEPTIC ULCER

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AND
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The impression that bleeding ulcers do not perforate and ulcer perforations do not bleed seems to be generally accepted by physicians and surgeons as true. That occurrence of bleeding and perforation together is uncommonly encountered is inferred from references stating that it is well known that bleeding ulcers rarely perforate and vice versa [1] or that bleeding and perforation rarely occur together.[2] Finsterer,[3] in a vast experience, reported finding hemorrhage and perforation occurring together only three times. Blackford and his associates [4] concluded "bleeding ulcers don't perforate; and ulcer perforations don't bleed." James and Matheson,[5] however, reported hemorrhage in the presence of perforation of a peptic ulcer and, again, hemorrhage which followed surgical resection of a peptic ulcer. They questioned the validity of the accepted impression.

Bleeding that occurs with peptic ulcer may be described as massive, moderate or slight. The massive hemorrhage is usually sudden in onset and produces the clinical picture of shock, faintness, weakness, rapid pulse, pallor and signs of collapse. Loss of consciousness may occur. Vomiting often follows if the stomach is sufficiently distended or if obstruction to the outlet is present. The vomitus may be described as "blood," "bloody vomitus," "coffee-ground vomitus" or "vomitus stained with blood." The patient is usually able to describe the quantity and consistency. If, however, there is no vomiting, the blood lost is passed as melena. The observing patient will note the black or tarry consistency of the stool, but the unobserving patient may describe the attack he experienced as a fainting spell and allow it to pass as such. Moderate amounts of bleeding more frequently will pass unnoticed. The symptoms of the patient will then be chiefly those of anemia. Pallor may be noted. Exercising may cause palpitation, rapid pulse or dyspnea, or the patient may feel more easily fatigued than formerly. Weakness may be the chief complaint. The character of the stools will be most important, however, and usually gives the clue. Slight amounts of bleeding are usually not detected and are discovered only by a careful history, physical examination or laboratory tests.

Early peptic ulcers that are produced experimentally are covered with a thin gray homogeneous membrane.[6] Removal of this membrane at the site of the beginning ulcer by a gentle sponging causes profuse bleeding. After the process has eroded the mucosa, it may proceed until the entire wall of the intestine is perforated. The time necessary for an ulcer to develop may be short. The mucosa may be penetrated in a few hours or more. Perforation may occur in a relatively short time after the mucosa has been penetrated. An ulcer may present the typical appearance of a chronic ulcer after three weeks, and an ulcer that is 5 months old may have the gross appearance of an ulcer 1 month old.

It is conceivable, therefore, that in a patient with a peptic ulcer the lesion may become active and cause further ulceration and perforation. This may occur with the patient who gives a brief history of symptoms but has had no management instituted. It may occur with a patient who has had an ulcer for some time, has had it controlled and has been placed under ambulatory management, or it may occur in a patient who has been resistant to management and treatment but has reached the stage where the healing processes are slowly progressive. The ulcerating process may proceed to bleeding by digestion of a thrombus from a previously thrombosed vessel or by erosion of blood vessels that may lie in the deeper structures of the ulcer crater. The amount of bleeding that follows will depend on the size and character of the blood vessel that is eroded, followed by the rapidity of the patient's reparative processes. Perforation, if it should occur, demands no delay in treatment.

In a partial review of the literature to note the incidence of hemorrhage in perforated peptic ulcer, Eliason and Ebeling[7] collected 240 cases from the literature and found a history of previous hemorrhage twenty-four times. They added to this frank hematemesis in the past history in nine of fifty-four cases and melena in nine of fifty-one cases. Hematemesis at the time of actual perforation was observed four times. Shawan [8] reported 227 cases, in seventeen of which there was a history of bloody vomitus, and blood was recorded in the examination of the stool eleven times. Rhodes and Collins [9] reviewed 155 cases, in two of which there was a history of coffee-ground vomitus, but in no case was hematemesis or melena recorded. McCreery [10] reported 170 cases, in five of which there was hematemesis and in thirteen tarry stools. Mondor and Lauret [11] noted hematemesis once in seventy-five cases of perforated gastric ulcer. In seventy-five cases of perforated duodenal ulcer abundant hematemesis was reported in two cases and blood-tinged vomitus in two cases.

Raven [12] reported melena twice and hematemesis once in a series of eighty cases. White and Patterson, quoted by Brenner,[13] reported bleeding in 3 per cent of sixty-two cases. Jirásek and Persky [14] noted fresh blood or coffee-ground material in the vomitus of seven patients in a series of eighty. James and Matheson [5] stated that they had seen bleeding and perfora-

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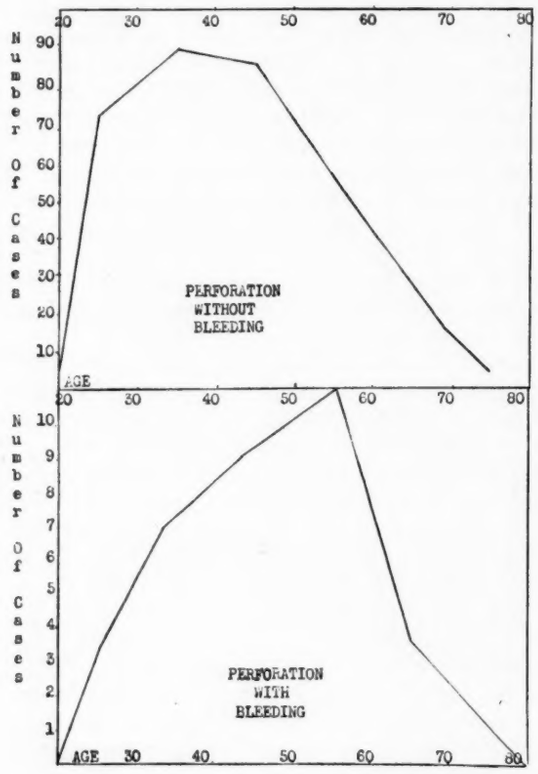
2. Berg, Benjamin N.: The Coexistence of Perforated and Bleeding Duodenal Ulcers, S. Clin. North America **11**: 543 (June) 1931.
3. Finsterer, H.: Die operative Behandlung der akuten profusen Magen- und Duodenalblutungen, Wien. klin. Wchnschr. **44**: 1125 (Sept. 4), 1160 (Sept. 11), 1185 (Sept. 18) 1931.
4. Blackford, J. M.; Smith, Alfred L., and Affleck, Dean H.: Peptic Ulcer Emergencies, Am. J. Digest. Dis. & Nutrition **4**: 646-650 (Dec.) 1937.
5. James, T. G. I., and Matheson, N. M.: Acute Perforation of Peptic Ulcer, Lancet **1**: 945-946 (May 5) 1934.
6. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, Am. J. Surg. **11**: 531-543 (March) 1931. Mann, Frank C., and Bollman, Jesse L.: Experimentally Produced Peptic Ulcers, J. A. M. A. **99**: 1576 (Nov. 5) 1932.
7. Eliason, E. L., and Ebeling, Walter W.: Catastrophes of Peptic Ulcer, Am. J. Surg. **24**: 63 (April) 1934.
8. Shawan, Harold K.: Acute Perforated Gastric and Duodenal Ulcers, Ann. Surg. **98**: 210-220 (Aug.) 1933.
9. Rhodes, George K., and Collins, Donald C.: Acute Perforated Peptic Ulcers, California & West. Med. **39**: 173 (Sept.) 1933.
10. McCreery, John A.: Perforated Gastric and Duodenal Ulcer, Ann. Surg. **107**: 350-358 (March) 1938.
11. Mondor, Henri, and Lauret, Gaston: Les ulcères perforés de l'estomac et du duodenum, Paris, Masson & Cie, 1923, p. 73.
12. Raven, R. W.: Perforated Gastric and Duodenal Ulcers, St. Barth. Hosp. Rep. **63**: 199-249, 1930.
13. Brenner, Edward C.: Perforated Ulcers of the Duodenum, Ann. Surg. **102**: 185 (Aug.) 1935.
14. Jirásek, A., and Persky, M. A.: A Study of Eighty Cases of Acutely Perforated Gastric and Duodenal Ulcers, Rhode Island M. J. **11**: 40-43 (March) 1928.

tion twice in seventy-five cases. Deaver and Pfeiffer [15] noted hematemesis and melena twice in fifty-five cases. Hematemesis at the time of actual perforation was observed four times. Mitchell [16] encountered hemorrhage three times in a series of fifty cases. Brenner [13] reported a history of melena four times with no hematemesis and melena in a series of fifteen cases.

Blackford and Baker [17] noted massive hemorrhage at the time of perforation in one instance in twenty-one cases. They also stated that slight hematemesis is common. Shawan and Vale [18] reported one case with hematemesis and melena in a series of ten cases. Horsley [19] noted no mention of recent bleeding in eight cases, and in only one of these was there any bleeding at all—hematemesis nine months before. Morrison [20] reviewed 200 cases and recorded no bleeding.




Age incidence of perforated peptic ulcer

The percentage of hemorrhage varies from 1.5 to 18 in the cases reviewed, with an average of 8. From the reviews the relation of the peptic ulcer history of the patient to the hemorrhage, whether by hematemesis or melena, is not evident. Further, the relation of the hemorrhage and ulcer to perforation cannot be elicited. Whether or not one is to defend the statement "bleeding ulcers do not perforate and ulcer perforations do not bleed" depends greatly on what history can be obtained from the patient relative to ulcer activity, hemorrhage and perforation. A significant history should give the connected story of the patient from incipience of his ulcer syndrome to its termination and the sequence of events that intervene.

With these thoughts in mind, we reviewed the records of patients with a diagnosis of perforated peptic ulcer who were admitted to Cook County Hospital for the period 1935-1938 inclusive to note the incidence of hemorrhage. Some of these patients had been treated in the various charitable clinics of Chicago prior to the time of their perforation. Many had been patients in the Cook County Hospital at some previous time and, at the time the accident happened, were being treated in the outpatient clinic maintained by the hospital. Other patients had not previously been attended by any physician.

Only patients with histories of peptic ulcer as the essential lesion were selected. Those with a history of some other disease as the essential diagnosis, e. g. arteriosclerosis, cardiac disease, cerebral disease and hepatic disease, with peptic ulcer as the incidental lesion, were not considered.

The diagnosis was made by the usual accepted history and physical evidence of a perforated ulcer. The operative report of repair of a peptic ulcer or report of a perigastric abscess [21] confirmed the diagnosis in the majority of cases; the fluoroscopic demonstration of air under the diaphragm confirmed the diagnosis in a few cases. An autopsy was made when permission could be obtained.

In reviewing the histories an attempt was made to get a history of ulcer activity, bleeding and perforation that would be clinically significant. Bleeding was not necessarily the most important aspect of the case or even a grave complication, but it was of such amount that it was considered important to the welfare of the patient. A story of hematemesis and melena described as noted previously was considered evidence of bleeding. In many cases study of the stomach contents and stool by direct examination or by chemical tests confirmed the information obtained from the patient. When the history could be traced to what was considered unmistakable evidence of continued ulcer activity (as in the instance of a patient who, while under management, continued to bleed for thirty days with perforation during this period or of a patient who gave a history of hematemesis and melena at varying intervals for one year before entrance and who on entrance had a red blood count of 1,780,000 with perforation) we considered the patient in the group who had perforation with bleeding.

Twenty-two patients were grouped as doubtful. In their histories were such statements as "brown vomitus," "blood-streaked vomitus," "dark stools," "an occasional hematemesis" or "an occasional tarry stool." Several gave a history of bleeding, hematemesis or melena one month or more before their admission. These patients were grouped with those who had nonbleeding perforated ulcers.

The question of hemorrhage was further studied. The amount of bleeding that occurs with an ulcer varies. Patients who bleed severely enough to produce faintness, syncope, rapid pulse, weakness, pallor and signs of shock are usually sufficiently alarmed to be seen by a physician immediately. The amount of hematemesis is estimated by the patient and all too frequently greatly exaggerated. The question of melena is different. The quantity of blood can in no wise be estimated, for the patient can only say that the stool was black

15. Deaver, John B., and Pfeiffer, Damon B.: Gastro-Enterostomy in Acute Perforated Ulcer of the Stomach and Duodenum, Ann. Surg. **73:** 441 (April) 1921.

16. Mitchell, Edward D., Jr.: Symptoms of Perforated Peptic Ulcer, J. Tennessee M. A. **29:** 419 (Nov.) 1936.

17. Blackford, John M., and Baker, Joe W.: Acute Perforating Peptic Ulcer, Am. J. Surg. **12:** 18-22 (April) 1931.

18. Shawan, Harold K., and Vale, C. Fremont: Acute Perforation of Duodenal Ulcer, Ann. Surg. **78:** 342 (Sept.) 1923.

19. Horsley, Gay W.: Report of Eight Consecutive Cases of Ruptured Gastroduodenal Ulcers, Virginia M. Monthly **58:** 386-390 (Sept.) 1931.

20. Morrison, William R.: Two Hundred Acute Perforated Ulcers of Stomach and Duodenum, from Boston City Hospital, New England J. Med. **213:** 447 (Sept. 5) 1935.

21. Singer, Harry A., and Rosi, Peter A.: The Pathogenesis of Perigastric Abscess Complicating Peptic Ulcer, Am. J. M. Sc. **183:** 600-608 (May) 1932.

or of a tarry consistency. Many state that they have suffered no ill effect from such hemorrhage or, at most, only weakness. A question arose as to how much bleeding is necessary to produce a tarry stool but there were no available data to answer it.

A volunteer went on a control diet of milk and cream for twenty-one days and took measured quantities of whole human blood at three day intervals. On such a regimen it was found that 10 cc. of blood caused no noticeable change in the color of the stool. From 20 to 30 cc. turned the stool a brown color which was easily differentiated from the light color of the stool with a milk and cream diet but which could have passed for a normal variation of color from that with a general diet. From 40 to 50 cc. turned the stool progressively darker, so that it would have appeared abnormal even when compared with the variation of a normal diet. However, 60 cc. was required to turn the stool indisputably tarry in color and consistency. With a general unrestricted diet the results were substantially the same, that is, 30 cc. passed as producing a normal variation in color and 40 and 50 cc. as giving a color distinctly darker than normal, but 60 cc. was required to turn it tarry black. It would seem, therefore, that the very minimum amount of blood a patient loses when he has a tarry stool would be between 50 and 60 cc. Clinically this figure probably varies considerably, for experimentally the blood was all taken at one time and only a relatively small amount of the stool turned black. Further studies on the question are being conducted and will be reported at a later date.

TABLE 1.—*Sex Incidence in 361 Cases of Perforated Peptic Ulcer from 1935 to 1938 Inclusive*

| Sex | Total Cases | Without Bleeding | With Bleeding |
|---|---|---|---|
| Male | 352 | 320 | 32 |
| Female | 8 | 5 | 3 |
| Unrecorded | 1 | 0 | 1 |
| Total | 361 | 325 | 36 |

During the years 1935-1938 inclusive 361 patients were admitted to the Cook County Hospital with a diagnosis of perforated peptic ulcer. Of these thirty-six gave histories of bleeding and perforation. Figures for the total number of patients with peptic ulcers admitted for this period are not available. However, for the years 1937-1938, 1,352 patients were admitted with a diagnosis of peptic ulcer, 189 of whom had a perforated peptic ulcer, approximately 50 per cent of the total series for the four year period.

A summary of the differences with respect to age, sex, incidence of perforation and hemorrhage, duration of symptoms and position of the ulcer has been made.

The predominance of the male sex is marked. The ratio agrees generally with statistics from other large charitable clinics.[22] However, this is in contrast to the statistics of Hale and White [23] and others quoted by Graves,[24] who found that perforation was twice as common in women as in men. In a recent review of autopsy records at Cook County Hospital, Portis and Jaffé [25] found the ratio of essential peptic ulcer lesions in male and female patients to be approximately 8:1, respectively. Hurst and Stewart [23] found a ratio of approximately 2:1. The incidence of peptic ulcer appears to be increasing in males.

The age incidence of perforation and bleeding is of interest. The greatest number of perforations occurred in the fourth decade, although the figures for the third, fourth and fifth decades approximate one another closely. Following this peak there is a sharp decline to the base line. Bleeding with perforation reached its highest incidence in the sixth decade, approximately twenty years after the incidence of the greatest number of perforations. Arteriosclerosis, either general or localized, is the most probable cause for this variation.

TABLE 2.—*Age Incidence of Perforated Peptic Ulcer*

| Age, Years | Total Cases | Without Bleeding | With Bleeding |
|---|---|---|---|
| 16-20 | 5 | 5 | 0 |
| 21-30 | 75 | 72 | 3 |
| 31-40 | 97 | 90 | 7 |
| 41-50 | 95 | 86 | 9 |
| 51-60 | 63 | 52 | 11 |
| 61-70 | 16 | 12 | 4 |
| Over 70 | 5 | 3 | 2 |
| Unrecorded | 5 | 5 | 0 |
| Total | 361 | 325 | 36 |

A total of 152 perforated ulcers were found in the stomach. Of these 136 occurred as perforation with no bleeding. Sixty-one were located on the anterior surface of the pylorus and prepylorus, twenty-eight on the lesser curvature of the stomach and four on the posterior wall of the pylorus. Forty-three ulcers were listed as unclassified because the description of the location was ambiguous. While it was felt that the lesion was located on the anterior surface of the pylorus and prepylorus most often, it was not definitely so stated. Sixteen occurred with perforation and bleeding. Nine were situated on the anterior surface of the pylorus and prepylorous, three on the lesser curvature of the stomach and, again, four were unclassified.

TABLE 3.—*Site of the Ulcer*

| | Without Bleeding | | With Bleeding |
|---|---|---|---|
| | Number | Per Cent | |
| Stomach | | | |
| Anterior wall pylorus | 61 | 44.9 | 9 |
| Lesser curvature | 28 | 20.6 | 3 |
| Posterior wall pylorus | 4 | 3.0 | 0 |
| Unclassified* | 43 | 31.5 | 4 |
| Total | 136 | 100.0 | 16 |
| Duodenum | | | |
| Anterior wall | 105 | 60.8 | 8 |
| Posterior wall | 7 | 4.0 | 0 |
| Second portion | 2 | 1.2 | 1 |
| Unclassified* | 58 | 34.0 | 7 |
| Total | 172 | 100.0 | 16 |
| No operation | 10 | .... | 2 |
| Recorded as peptic | 4 | .... | 1 |
| Abscess found [21] | 3 | .... | 1 |

* "Unclassified" included terms such as "duodenal ulcer" "peptic ulcer" and "gastric ulcer" without specific description as to its location; that is, the description was equivocal.

A total of 188 perforated ulcers were found in the duodenum, 172 of which occurred as perforation without bleeding. The anterior surface was perforated 105 times, the posterior wall seven times and the second portion twice. Again, fifty-eight were listed as unclassified. Sixteen ulcers perforated and bled. Eight of these occurred on the anterior surface of the duodenum and one on the second portion, and seven were unclassified.

22. Shawan.[8] Blackford and others.[4] Deaver and Pfeiffer.[15] Morrison.[20]

23. Hurst, Arthur F., and Stewart, Matthew J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929.

24. Graves, Amos M.: Perforated Peptic Ulcers in German Clinics, Ann. Surg. **98**: 197-209 (Aug.) 1933.

25. Portis, Sidney A., and Jaffé, Richard H.: A Study of Peptic Ulcer Based on Necropsy Records, J. A. M. A. **110**: 6 (Jan. 1) 1938.

Twelve patients were treated medically, ten for perforation without bleeding and two for perforation and bleeding. Five patients were recorded as having peptic ulcers, four with perforation and no bleeding and one with perforation and bleeding. Four patients were found to have a perigastric abscess, one of whom bled.

There were more ulcers located on the anterior surface of the stomach (nine) and duodenum (eight) that perforated and bled than elsewhere. The ratio of perforation to perforation and bleeding appears to be approximately the same for the ulcers that are located on the anterior wall and for those on the lesser curvature of the stomach. However, one should not lose sight of the fact that many more ulcers are located on the lesser curvature than on the anterior surface of the stomach. This ratio, then, has little significance.

There are certain anatomic peculiarities about the anterior wall of the pylorus and the first portion of the duodenum, where the great majority of perforating ulcers occur. The areas immediately proximal and distal to the pylorus possess a deficient circulation.[26] The arteries of the submucosa in the pyloric region of the inferior portion of the lesser curvature are practically terminal vessels and are sparsely distributed, thus giving a limited blood supply to this area.[27] These arteries are tortuous, anastomose infrequently and are subject to powerful and repeated constrictions by the musculature of the stomach. Reeves [26] stated that he considered the lesser curvature as spreading out to include practically the entire pylorus. He found that because of their anatomic arrangement the arteries along the lesser curvature of the stomach and the first inch of the duodenum are predisposed to thrombosis. The branches from the arterial plexus along the lesser curvature run a highly tortuous course to enter the mucosa; therefore the resistance offered the blood stream is constantly greater and, as a result, the blood current as it enters the smaller arteries of the mucosa is slower.

TABLE 4.—*Duration of Symptoms*

| Duration | Total Cases | Without Bleeding | With Bleeding |
|---|---|---|---|
| No history | 51 | 48 | 3 |
| Under 2 months | 39 | 36 | 3 |
| 2-12 months | 52 | 47 | 5 |
| 1-2 years | 23 | 21 | 2 |
| 2-5 years | 46 | 39 | 7 |
| Over 5 years | 56 | 50 | 6 |
| Unrecorded* | 94 | 84 | 10 |
| Total | 361 | 325 | 36 |

* "Unrecorded" includes terms like "years," "months," " a long time."

The rather limited blood supply, the tortuosity of the vessels and the resistance offered the blood stream by the constrictions of the musculature predispose to thrombosis.

Wilkie [28] has called attention to the variability of the origin of the blood vessels supplying the duodenum. No other data could be found relative to the variation that may occur in the course of the coronary arteries or major branches thereof of the stomach and duodenum. Anson [29] is now conducting research on this question, but the work has not progressed far enough to be of value at present. The deficiency in blood supply perhaps explains the frequency of perforation on the anterior surface of the stomach and duodenum. Hemorrhage occurred in approximately 13 per cent of the perforations of the stomach and 8 per cent of the perforations of the duodenum. This may be explained when the relative variation that may occur in the blood supply to these areas is known.

26. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, Surg., Gynec. & Obst. **30:** 374 (April) 1920.
27. Einhorn, Moses: Anatomical Considerations of the Ulcer Bearing Area, Surg., Gynec. & Obst. **50:** 416 (Feb.) 1930.
28. Wilkie, O. P. D.: The Blood Supply of the Duodenum with Special Reference to the Supraduodenal Artery, Surg., Gynec. & Obst. **13:** 399, 1911.
29. Anson, Barry J.: Personal communication to the authors.

### PATHOLOGIC CONSIDERATIONS

Thirteen patients who had perforation without bleeding came to autopsy. Eight had a single ulcer on the anterior surface of the first part of the duodenum. Two had single ulcers on the lesser curvature of the stomach. One patient had three ulcers, of which two were on the anterior surface of the stomach and the third was on the posterior surface of the duodenum. One patient had two ulcers of the stomach, one on the anterior surface and the other on the lesser curvature. The last patient had two ulcers of the duodenum, of which one was on the anterior wall and the other on the posterior wall. Thus three patients had multiple ulcers.

Eight patients who had perforation with bleeding came to autopsy. Seven of these had multiple ulcers; the eighth had a single ulcer on the lesser curvature of the stomach. Of the seven patients who had multiple lesions, one had five ulcers of the stomach, two had ulcers of the stomach and duodenum coexisting and another had multiple erosions of the esophagus and a duodenal ulcer. Three patients had two ulcers of the duodenum; in each case one ulcer was located on the anterior wall and the other on the posterior wall. In two of the latter cases the perforation occurred in the anterior ulcer and hemorrhage from the posterior. The source of bleeding in the remainder was not determined.

The possibility of two or more ulcers must be borne in mind. Gastric ulcers situated on one surface of the stomach may be complicated by an ulcer on another surface of the stomach or by ulcerations elsewhere in the esophagus or bowel. Duodenal ulcers seldom occur with gastric ulcers. Perforation of an ulcer on the anterior surface of the duodenum or stomach has been followed by fatal hemorrhage from an ulcer on the posterior surface of the duodenum or stomach.[30] Multiple ulcers have been reported as varying from 18 to 30 per cent in series of perforated ulcers.[31]

The records of nine patients with multiple ulcers were critically reviewed for notes indicating the nature of the pathologic condition that existed prior to autopsy. For two patients surgical repair of the perforation was made. The pathologic picture of one patient was adequately described at operation and no further comment on the gross pathologic changes was made at autopsy. With regard to the other patient, a perforated ulcer located on the anterior surface of the viscus was adequately described but an ulcer located posteriorly was not mentioned.

The remaining seven patients entered the hospital in a serious condition. It was suspected that four had an ulcer perforation, but the condition of each was such that surgical treatment would have been only an added burden to their grave illness. The condition of three patients was undiagnosed. Multiple ulcers in the latter

30. Wright-Smith, R. J.: Peptic Ulcer: An Analysis of 218 Cases Studied at Autopsy, M. J. Australia **2:** 1027-1031 (Dec. 11) 1937. Raven,[12]
31. Fishback, H. R.: Personal communication to the authors. Graves,[21] Wright-Smith.[30]

were not mentioned, although the bleeding from the gastrointestinal tract was a prominent part of the clinical picture.

Microscopic sections were examined in several instances. In each the chronic type of ulcer with sclerous connective tissue base was found. The muscularis was replaced by scar tissue. Round cell infiltration was noted in each section, and eosinophils were infrequent. The base was avascular, and the vessels that were situated here had thick sclerotic walls. The arteries in the neighboring submucosa, muscularis and subserosa had thickened walls. The endothelial lining often showed proliferation, and in at least two instances fairly large arteries were thrombosed. In some cases young granulation tissue was found near the edge of the ulcer. There was a gradual histologic change from the normal tissue surrounding the ulcer process to the sclerotic alterations found in the base of the ulcer. No sections indicative of an acute process were noted.

This study would support those who believe perforation occurs more often in the chronic type of ulcer than in the acute.[32] Dible [33] stated that bleeding is more common in the acute type than in the chronic type and that when perforation occurs in the latter it is due to an unusually active process. Behrend [34] suggested that perforation occurs in the chronic type of ulcer with a firm sclerotic base and that hemorrhage occurs in the acute type with soft congested edges.

Fifty-one patients (table 4), or 14 per cent, gave no history of symptoms or signs of peptic ulcer prior to their admission for perforation. This is in accord with other reviews.[35] Further, there is little variation in the ratio of perforation with the period of symptom-activity.

TABLE 5.—*History, Hemorrhage and Perforation of Ulcers* *

| Age, Years | Sex | Duration of History | Duration of Bleeding | Hematemesis and Melena | Location of Perforation and Postmortem Observations |
|---|---|---|---|---|---|
| 28 | ♂ | 4 years | 1 day | Tarry stools | Duodenal ulcer |
| 32 | ♂ | Unrecorded | 1 day | Hematemesis on admission | Anterior wall pyloroduodenal junction |
| 38 | ♂ | Unrecorded | 1 day | Hematemesis 1 hour | Prepyloric ulcer |
| 38 | ♂ | 7 years | 1 day | Tarry stools prior to entrance | Second portion of duodenum |
| 46 | ♂ | Unrecorded | 1 day | Tarry stool | Anterior wall pylorus |
| 47 | ♂ | 18 months | 1 day | Coffee-ground hematemesis; black stool | Duodenum |
| 50 | ♂ | Unrecorded | 1 day | Stomach contents gross bleeding | First part duodenum, superior surface |
| 56 | ♂ | Unrecorded | 1-2 days | Black or bright red stools | Anterior wall duodenum |
| 72 | ♂ | 6 years | 1 day | Black stool | Prepyloric lesser curvature |
| 26 | ♂ | 6 months | 2-3 days | Black, tarry stools 2-3 days | Anterior surface pylorus |
| 55 | ♂ | 4 years | 3 days | Melena 3 days | Middle third lesser curvature of stomach |
| 57 | ♂ | Unrecorded | 3 days | History of vomitus and aspirated blood prior to entrance | Anterior wall upper edge of duodenum |
| 34 | ♂ | 3-4 days | 3-4 days | Tarry stools 2-3 days | Anterior surface pyloric end of stomach |
| 53 | ♂ | 3-4 years | 4½ days | Hematemesis, melena, vertigo, weakness | Post mortem: 2 duodenal ulcers; first on anterior wall, 10 mm. diameter; second on posterior wall, 1 cm. diameter |
| 45 | ♂ | 3 weeks | 7 days | Tarry stools, occult blood 4 plus | Anterior wall pylorus |
| 48 | ♂ | 7 years | 7 years | Tarry stools 7 days | Post mortem: anterior wall duodenum, multiple erosions of esophagus |
| 60 | ♂ | Unrecorded | 7 days | Tarry stools 7 days | First portion duodenum |
| 42 | ♀ | 7-10 days | 7-10 days | Tarry and black stools | Perforated peptic ulcer |
| 55 | ♂ | 6 months | 8 days | Coffee-ground vomitus first, third and eighth day; tarry stool daily for seven days | Anterior wall pylorus |
| 35 | ♂ | 5-6 years | 10 days | Tarry stools 10 days | Duodenal ulcer |
| 49 | ♂ | Unrecorded | 14 days | Hematemesis 2 weeks | Perigastric abscess |
| 57 | ♂ | 2 years | 14 days | Fainting 14 days; black, tarry stools | Duodenal ulcer |
| 65 | ♂ | 4 years | 14 days | Tarry stools 2 weeks before entry | Fluoroscope: free air under diaphragm |
| 27 | ♀ | Unrecorded | 21 days | Coffee-ground vomitus, red blood hematemesis; tarry stools | Post mortem: 4 peptic ulcers; 3 gastric, 1 perforated; 1 duodenual |
| 47 | ♂ | 3 years | 21 days | Tarry stools 21 days | Anterior wall duodenum |
| 53 | ♂ | 21 days | 21 days | Tarry stools 21 days, guaiac test 2 plus | Post mortem: 2 ulcers duodenum; 1 anterior wall perforated, 1 posterior wall hemorrhage severe |
| 33 | ♂ | Unrecorded | Unrecorded | Tarry stools, 3 plus occult blood | Post mortem: 2 duodenal ulcers; 1 perforation anterior wall first part of duodenum; second on posterior wall |
| 53 | ♂ | 1 year | Unrecorded | Black stools, positive guaiac test | Post mortem: 5 gastric ulcers, 1 anterior wall perforation, 4 on lesser curvature |
| 73 | ♂ | Unrecorded | "Few" days | Small tarry stool | Prepyloric ulcer |
| 39 | ♂ | 10 years | 30 days | Bleeding ulcer 30 days, hospital treatment for blood loss | Lesser curvature duodenum |
| 55 | ♂ | Unrecorded | 42 days | Vomited blood present history; tarry stools 42 days, 4 plus occult blood 21 days | Anterior surface pylorus |
| 50 | ♂ | 15 years | 72 days | Connected history vomiting blood and having black stools | Anterior wall lesser curvature duodenum; gastric, anterior wall pyloric |
| 64 | ♂ | 3 years | 3 months | Bloody vomitus; 2 plus benzidine in stools | Post mortem: perforation superior border stomach, saddle-shaped ulcer, also ulcers of colon |
| 66 | ♂ | 4 months | 3-4 months | Black stool | One inch above pylorus |
| 55 | ♂ | 4 years | 142 days | Vomited bright red blood; occult blood in stool 4 plus | Anterior surface duodenum |
| 64 | ♀ | 1 year | 1 year | Recurring coffee-ground vomitus and tarry stools 1 year; red cell count 1,780,000 | Post mortem: lesser curvature of stomach, 1 cm. from pylorus |

* Fourteen patients (aged from 26 to 72) had a history of hemorrhage from one to six days before perforation. Nine patients (aged from 35 to 55) had a history of from seven to fourteen days' duration. Thirteen patients (aged from 27 to 73) had a history of fifteen days' duration or more.

Examining the thirty-six patients with hemorrhage and perforation (table 5), it will be noted that fourteen patients had bleeding from one to six days prior to perforation. The majority of patients manifested this by the character of the stools. A few noted hematemesis. In one patient multiple erosions of the esophagus, as well as an ulcer of the duodenum, were found at autopsy. The condition of this patient at the time of entrance to the hospital was such that surgical intervention was contraindicated. The origin of the bleeding may be questioned. It may have originated from the esophageal erosions. However, from the data

32. Tammann, H., and Ludewig, H. H.: Zur Morphologie des frei perforierten Ulcus Duodeni, Zentralbl. f. Chir. **64**: 2769 (Dec. 4) 1937. Hurst and Stewart.[23] Behrend.[34] Wright-Smith.[30]

33. Dible, J. Henry: The Pathology of Gastric Ulcer, Surgery **2**: 675-691 (Nov.) 1937.

34. Behrend, Moses: Incidence of Hemorrhage in Perforated Gastric and Duodenal Ulcers, J. A. M. A. **95**: 1889-1892 (Dec. 20) 1930.

35. Meyer, K. A., and Brams, W. A.: Acute Perforation of Gastric and Duodenal Ulcer, Am. J. M. Sc. **171**: 510 (April) 1926. Eliason and Ebeling.[7] Deaver and Pfeiffer.[15] Shawan and Vale.[19]

reviewed, the duodenal ulcer played an important part in the production of the symptom complex. Neither the age of the patient nor the duration of the ulcer history made any difference in the tendency to hemorrhage and perforation. It occurred in all decades after the second. Nine patients noted hemorrhage from seven to fourteen days before perforation. Again, the tendency to bleeding perforation occurred with the same abandon as noted in the earlier group. Thirteen patients noted bleeding fifteen days or more prior to perforation. It is in this group that the history of intermittent or recurrent bleeding is noted. One patient who was bleeding was thought to be immune to perforation because "bleeding ulcers do not perforate." Also the multiple ulcers are found more frequently. The repeated loss of blood seems to play a part in lowering the resistance of the patient to the factors responsible for ulceration of the bowel. Sufficient bleeding to produce tarry or black stools was noted in the majority of patients prior to symptoms indicating perforation. The amount of blood lost can in no wise be determined. It would seem, then, that a patient with a known ulcer history who suddenly manifests signs of hemorrhage should be looked on as a candidate for a more serious and grave complication of ulcer—perforation.

Statistics on the incidence of hemorrhage in peptic ulcer vary considerably and for this reason are difficult to evaluate. When one adds to them the statistics on the incidence of perforation, the task becomes increasingly difficult. The total number of ulcer patients for the four year period 1935-1938 inclusive are not available. However, during this period 361 patients who had peptic ulcers with perforation were admitted, and thirty-six of them, approximately 10 per cent, had a history of bleeding preceding the perforation. For two years of the period (1937 and 1938) 1,352 patients with peptic ulcer were admitted, and of these 189 had perforation. Applying the percentages to the latter group, one finds that approximately 1 per cent of the patients with peptic ulcer bled and perforated. While this group may be too few in number for one to draw any conclusions, it might be better to say that bleeding and perforation occur in approximately 1 per cent of peptic ulcers than to say "bleeding ulcers don't perforate and ulcer perforations don't bleed."

### SUMMARY AND CONCLUSIONS

Three hundred and sixty-one patients with perforated peptic ulcer that entered Cook County Hospital during the years 1935-1938 inclusive were reviewed to note the incidence of hemorrhage. Bleeding and perforation in a peptic ulcer do occur together. For the four years reviewed, bleeding was present in 10 per cent of the patients with perforated ulcer, and bleeding and perforation occurred in approximately 1 per cent of all patients admitted with the diagnosis of peptic ulcer during the years 1937 and 1938. Approximately 60 cc. or more of blood has escaped into the bowel when a patient has melena. Perforation in peptic ulcers occurred more often in males than in females. It occurred most frequently in the fourth decade, although the fifth decade showed almost the same number of cases. Bleeding and perforation occurred most frequently together in the sixth decade. Hemorrhage that follows surgical repair of a perforation should arouse suspicion that an ulcer situated elsewhere in the gastrointestinal tract may be responsible for the bleeding.

30 North Michigan Avenue.

# PRIMARY TUBERCULOUS INFECTION ATTACK RATES

## OBSERVATIONS FOR SELECTED LOCAL POPULATION GROUPS

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The observations reported in this paper were made recently on a total of 3,868 persons representing five different groups included in the population of Minneapolis and St. Paul (summarized in the accompanying table). The data obtained reveal the existence of wide variations in the current rates at which different groups are acquiring infections with tubercle bacilli. Analysis of these observations is undertaken for the purpose of demonstrating which of the surveyed groups experienced an exceptionally high infection rate which can be greatly reduced. The general significance of our observations presumably is proportional to the degree to which the records for each group studied are representative of the experience in comparable groups residing elsewhere.

During the course of an epidemiologic survey conducted in private practice on the personnel of a series of household units,[1] 0.1 mg. of old tuberculin was administered intradermally to 1,278 children and to 1,192 of their respective parents.

When tested at an average age of 6.4 years, 5.2 per cent of the children proved to be sensitive to tuberculoprotein. From these records it is evident that infection with tubercle bacilli had been acquired by about 0.8 per cent of the group annually. This relatively low crude annual contamination rate is used here as a standard with which the annual infection rates observed for other groups whose records appear in the table are compared. In order to facilitate these comparisons, an arbitrary value of 1 is assigned to the crude annual primary tuberculous infection attack rate [2] recorded for the 1,278 children surveyed in private practice.

The data for the 1,192 parents included in this study show that 57.6 per cent were sensitive to 0.1 mg. of the old tuberculin when tested at an average age of 36.3 years. According to these observations, this group of adults had acquired infection with tubercle bacilli at a crude average rate of about 1.6 per cent annually. Since the annual primary infection attack rate recorded for these parents is double the average contamination rate observed for their children, the latter apparently have been exposed to roughly one half the mean effective infection risk that the former faced. Whether these observations reflect the general trend during the past three decades in the tuberculous infection risk prevalent in Minneapolis homes of the type represented in this study or reveal a current difference in the frequency with which children and their respective parents are now being exposed to open cases of tuberculosis is an interesting and speculative question. Observations published recently by Harrington, Myers and Levine [3]

From the Departments of Pediatrics and of Preventive Medicine, University of Minnesota Medical School.

1. Stewart, C. A.: Periodic Accrediting of Households, Am. J. Dis. Child. **54**: 699 (Oct.) 1937.

2. The tuberculin reaction discloses primary infection with tubercle bacilli, but no comparable method for revealing reinfections has been devised.

3. Harrington, F. E., Myers, J. A., and Levine, N. M.: Significance of the Tuberculin Test, J. A. M. A. **108**: 1309 (April 17) 1937.

provide evidence to the effect that the rate at which Minneapolis children are infected with tubercle bacilli declined appreciably during a period of ten years.

Data collected by Myers, Diehl and their associates,[4] for 173 students who gave negative Mantoux reactions when they entered the college of education at the University of Minnesota show that 5.8 per cent became sensitive to tuberculin during their four year course of study. The average annual rate at which infections with tubercle bacilli were introduced into this series of young adults (1.5 per cent), like that (1.6 per cent) recorded for the parents included in this study, is practically double the crude primary tuberculous infection rate of 0.8 per cent obtained for the children whose records appear in the table. Although the environment of these children seems to have been safer on the average than that of students enrolled during the same decade in the college of education at the University of Minneapolis, nevertheless the tuberculous infection risk to which the latter were exposed recently probably can be rated as being comparatively low but susceptible probably to improvement.

A follow-up study conducted on 289 medical students who failed to react positively to 0.1 mg. of old tuberculin at the time they entered the college of medicine of the University of Minnesota disclosed that twenty-four, or 8.3 per cent, had become sensitive to this dose of tuberculoprotein by the time they had finished their junior year in school. During this three year period of study, which provided very little contact with patients and included no special tuberculosis service, 2.8 per cent of the group was infected each year. This crude annual primary tuberculous infection rate is three times that observed for the children whose records are used here as a basis for comparison.

According to the records of the Student Health Service at the University of Minnesota, 265 of the original group of 289 uninfected students continued to show negative reactions to 0.1 mg. of old tuberculin applied at the beginning of the senior year. During the last or clinical year of their course, the 265 young adults who started their senior year uncontaminated not only devoted much of their time to examining and treating patients but also spent two weeks on a special tuberculosis service. At the end of the senior year 118 members of the group were found to be sensitive to tuberculoprotein. The annual tuberculous infection rate observed for this group of medical students amounts to 44.5 per cent, which is sixteen times the annual rate noted for each of the first three years of their course of study and is fifty-six times the infection attack rate recorded in the table for Minneapolis children who were residing in private homes. Obviously an exceptionally high contamination risk was experienced by these medical students during their clinical or senior year.

Data have also been collected for a group of 276 student nurses who failed to react positively to 0.1 mg. of old tuberculin at the time they started a three year course of study in local private hospitals that maintain no beds for tuberculous patients. Of this group of 276 originally uncontaminated young adult girls, eighty-four, or 30.4 per cent, were found to be sensitive to 0.1 mg. of tuberculoprotein at the time of graduation. Roughly 10.1 per cent of the group had acquired infections with tubercle bacilli each year. This annual tuberculous infection rate is approximately twelve times that observed for the Minneapolis children whose records appear in the table. This observation is interpreted as evidence that a relatively high risk of acquiring infection with tubercle bacilli confronts nurses during their period of training in hospitals that maintain no special tuberculosis service. Apparently unrecognized human dissemination of tubercle bacilli are inadvertently admitted to institutions of this character with appreciable frequency. If these local records provide an approximate estimate of what is taking place in private hospitals throughout the country, it seems quite obvious that an important preventable but generally unappreciated health hazard exists in institutions that knowingly admit few or no tuberculous patients for treatment. The correction of this situation probably is contingent not on refusing to admit tuberculous patients to private hospitals but rather on adopting the general policy of practicing strict aseptic nursing technic in connection with the care and treatment of each patient admitted to a private hospital until Mantoux tests applied as a routine and subsequent roentgenologic, laboratory and clinical examinations of each infected tuberculin-sensitive patient demonstrate the absence of a readily communicable form of tuberculosis, particularly open chronic pulmonary tuberculosis or phthisis.

The tuberculous infection rate recorded for the nurses training in hospitals which maintain no special tuberculosis service was distinctly lower than that observed for other student nurses whose course included a period during which tuberculous patients were given care. The records for 344 student nurses who entered training with negative reactions to 0.1 mg. of old tuberculin and spent three years in hospitals which provided six weeks training in special tuberculosis wards show that 204, or 59.3 per cent, of the group had acquired infection

*Crude Annual Primary Tuberculous Infection Attack Rates for Different Local Population Groups*

| Source of Data | Environment During Period of Observation | Total Number | Time Spent in Environment, Years | Number and per Cent Infected During Time Spent in Environment | | Average Annual Increase in Infections (per Cent): "The Crude Annual Primary Infection Attack Rate" | Ratio of Each Infection Attack Rate to That Found for Minneapolis Children | Estimated Time Required for 100 per Cent of Each Group to Be Infected, Years |
|---|---|---|---|---|---|---|---|---|
| | | | | Number | Per Cent | | | |
| Children | Private homes | 1,278 | 6.4 | 67 | 5.2 | 0.8 | 1 | 125.0 |
| Parents | Private homes | 1,192 | 36.3 | 687 | 57.6 | 1.6 | 2 | 62.5 |
| Students | College of education | 173* | 4.0 | 10 | 5.8 | 1.5 | 2 | 66.7 |
| Medical students | Freshman, sophomore, junior years; no tuberculosis service | 289* | 3.0 | 24 | 8.3 | 2.8 | 3 | 25.0 |
| | Senior year; 2 weeks tuberculosis service | 265* | 1.0 | 118 | 44.5 | 44.5 | 56 | 1.6 |
| Nurses training in hospitals | No tuberculosis service | 276* | 3.0 | 84 | 30.4 | 10.1 | 12 | 9.9 |
| | Six weeks tuberculosis service | 344* | 3.0 | 204 | 59.3 | 19.8 | 25 | 5.4 |
| | Three months tuberculosis service | 158* | 3.0 | 141 | 89.2 | 29.7 | 37 | 3.4 |
| | Six weeks tuberculosis service | 158† | 10 weeks | 35 | 22.2 | 115.4 | 144 | 0.7 |

* Tuberculin reaction negative to 0.1 mg. of tuberculin when study was commenced.
† Tuberculin reaction negative to 1 mg. of tuberculin when study was commenced.

4. Myers, J. A.; Diehl, H. S.; Lees, H. D., and Levine, I.: Tr. Nat. Tubere. A., thirtieth annual meeting, Cincinnati, 1934, p. 345.

with tubercle bacilli during their three year course of study. The crude annual primary tuberculous infection rate observed for these students amounts to 19.8 per cent, which is nearly twice that recorded for nurses whose course of study provided no training in wards for tuberculous patients and is twenty-five times the rate recently experienced by Minneapolis children residing in private homes.

A follow-up study on an additional group of 158 student nurses who entered training with negative reactions to 0.1 mg. of old tuberculin and spent three years in hospitals whose course of study included three months' service in wards for tuberculosis patients disclosed that 141, or 89.2 per cent, of the group acquired infection with tubercle bacilli during a period of three years. The crude annual contamination rate observed for this group of young women is nearly three times the infection rate observed for nurses whose course included no special tuberculosis service and is thirty-seven times that recorded in the table for Minneapolis children. Attention is also called to the fact that the increases in infections recorded for the two groups of nurses who worked in wards for tuberculous patients were roughly proportional to the length of time each group spent in this type of service.

The high tuberculous infection attack rates recorded here for Minneapolis nurses whose course included a tuberculosis service are comparable to those reported by Geer [5] for groups of nurses also engaged in caring for tuberculous patients in hospitals in St. Paul. According to the data given in the accompanying table in Geer's communications, 75.9 per cent of 158 who entered training with negative reactions to tuberculin acquired infection with tubercle bacilli during an average period of about 1.1 years. For this group of nurses the annual primary infection attack rate (69 per cent) is approximately eighty-six times the rate observed for the Minneapolis children included in this study.

Although the data that have been considered up to this point show that infections are acquired at exceptionally high rates by those engaged in the care of tuberculous patients, nevertheless these observations are open to the objection that 0.1 mg. rather than 1 mg. of old tuberculin was used as a routine in determining whether infection with tubercle bacilli was absent or present. Fortunately, however, Dr. Ruth Boynton, director of the Student Health Service at the University of Minnesota, was able to provide observations on a group of 170 nurses who gave negative reactions to 1 mg. of old tuberculin immediately before they undertook a tuberculosis service of six weeks' duration. One hundred and fifty-eight of these nurses were retested four weeks after the special tuberculosis service was terminated; thus data are available which accurately reveal the true rate at which primary infections were acquired by the group during this brief period of contact with tuberculous patients. According to the data in the table, thirty-five, or 22.2 per cent, had made the transition from the uninfected to the infected state in a period of ten weeks. These nurses, therefore, experienced a primary tuberculous infection rate, which, computed on an annual basis, amounts to 115.4 per cent. This infection rate is 144 times the infection rate observed for the children whose records are used here as a basis for comparison. Since all these contaminations probably were acquired during the six weeks spent with tuberculous patients, it seems reasonable to attribute the 22.2 per cent increase in infections observed for these nurses to this short period of special training. When computed on this basis, the corrected annual primary tuberculous infection attack rate attributable to six weeks' contact with tuberculous patients amounts to 192 per cent, which is 240 times the contamination rate recorded in the table for Minneapolis children. The careful observations made on this group of 158 student nurses and the mutually confirmatory data for other groups whose records are included in this report are interpreted as conclusive evidence that infections with tubercle bacilli are acquired at exceptionally high rates by those who are engaged in the care of tuberculous patients. These observations also demonstrate that institutions maintained not only for the care of tuberculous patients but also for the purpose of protecting the public from contact infections by segregating disseminators of tubercle bacilli can serve as prolific centers of contagion where a large number of new human cultures of tubercle bacilli are produced annually if previously uncontaminated attendants are not given the protection of rigid aseptic measures. The serious consequences of infections acquired by students of nursing and medicine during their period of training has been reported recently by Myers and his associates.[6]

When follow-up studies disclosed the importance of the relatively unobtrusive health menace which confronts students registered in the college of medicine and nursing at the University of Minnesota, the faculty adopted measures designed to reduce this hazard to a minimum. These measures include the routine application of Mantoux tests to the professional and nonprofessional staffs of the hospital and periodic clinical and roentgenologic examinations of each tuberculin sensitive individual discovered in this manner. In addition, there was instituted the policy of observing aseptic technic in connection with the care of new hospital admissions until Mantoux tests and subsequent examinations of tuberculin sensitive patients excluded the presence of communicable forms of tuberculosis. Furthermore, a special tuberculosis service has been established by Dr. F. E. Harrington at the Minneapolis General Hospital, where attempts are being made to perfect a technic which will prevent attendants from acquiring infections with tubercle bacilli while working with tuberculous patients. The results of tuberculin tests periodically reapplied to previously uninfected persons during and after a period spent with tuberculous patients are expected to serve as an index of the efficiency of the prophylactic measures that are now being practiced. This follow-up study probably will reveal what is required to prevent those caring for patients with open cases of tuberculosis from being contaminated. The experience reported by Geer indicates that only the most rigid aseptic measures will prove adequate.

In order to obtain special information relative not only to the experience with tuberculous infection of students in other universities but also concerning precautions exercised elsewhere to keep this hazard at a minimum, a letter of inquiry was addressed to the deans of the medical schools of the United States and Canada. Replies to this communication received from forty-nine schools revealed that the problem is receiving very careful attention in some places but is largely neglected in other institutions. According to the reports

5. Geer, E. K.: Tuberculosis Among Nurses, Arch. Int. Med. **49:** 77 (Jan.) 1932; Am. Rev. Tuberc. **29:** 88 (Jan.) 1934.

6. Myers, J. A.; Diehl, H. S.; Boynton, Ruth E., and Trach, Benedict: Development of Tuberculosis in Adult Life, Arch. Int. Med. **59:** 1 (Jan.) 1937. Myers, J. A.; Trach, Benedict; Diehl, H. S., and Boynton, Ruth E.: Ann. Int. Med. **11:** 2181 (June) 1938.

received from several universities, the high rate at which their respective students of nursing and medicine are acquiring infection with tubercle bacilli is a question of deep concern to the faculty, and definite efforts are being made to correct the situation.

Reports submitted by a few universities in which the question of tuberculosis in students of medicine and nursing has been investigated indicate that this special health problem seems to be distinctly less important in some institutions than in others, and in some instances the local tuberculous infection risk was rated as inconsequential.

A general consideration of all the information supplied by the various medical schools of the United States and Canada suggests that the study of the rate at which infections with tubercle bacilli are being acquired by students of medicine and nursing, and the development of methods designed to reduce this menace to a minimum, are in their infancy. Several universities are planning a special investigation of local conditions; thus an increasingly exact concept of the prevalence and magnitude of this special health problem and also of the measures required for its solution may soon be available.

### CONCLUSION

The tuberculous infection risk prevalent in private hospitals and particularly in institutions that maintain wards for tuberculous patients constitutes a public health problem of sufficient importance to require careful investigation.

City Hall.

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## BURN SHOCK

### THE QUESTION OF WATER INTOXICATION AS A COMPLICATING FACTOR: BLOOD CHEMICAL STUDIES AND REPORT OF AN EXTENSIVE BURN TREATED BY REPEATED TRANSFUSIONS OF BLOOD AND BLOOD PLASMA

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It is common knowledge that cases of extensive burn are likely to terminate fatally. Seldom does recovery occur from a burn which involves half the body surface, even though the burn is superficial. There are many who die from burns involving considerably less than half the body surface. This is especially true of children.

Furthermore, it is known that patients with severe burns are liable to a variety of complications such as pneumonia, nephritis, embolism, perforating ulcer of the bowel, sepsis and various other pathologic states, any of which may be contributory causes of death. We mention these only to avoid possible confusion in the discussion which follows. Our principal theme concerns the acutely fatal shock reaction which comes a few hours or a few days after the burn.

The symptoms and course of the burn shock state are variable. Too often death comes unexpectedly in a case thought to be progressing favorably. With very large burns death comes quickly. The clinical picture is circulatory stasis progressing to a fatal termination.

The pulse becomes weak, and the blood pressure falls. The patient may be comfortable and often euphoric, so that the impending death is difficult to realize. Soon, however, the pulse cannot be palpated, the extremities become cold and livid or pallid with cyanosis, and the blood becomes thick and dark. The patient becomes stuporous and then comatose. Death terminates the picture within a few hours of the burn.

In the burned patient who lives for several days, the shock syndrome is more complicated. There may be pulmonary edema, vomiting, hyperpyrexia, progressive anasarca, convulsions and coma. Circulatory collapse terminates the course.

It is this latter group of symptoms which is usually ascribed to toxemia. The toxic theory has assumed that the burned flesh breaks down into poisonous split proteins which are absorbed into the circulation. It was this conception which led Davidson [1] to the tannic acid treatment with the thought of "fixing" toxins. Fluids were forced, to aid in the elimination.

It is now known that this theory is fallacious. Certainly the treatment based on it has not prevented death from burn shock.

### MECHANISM OF BURN SHOCK

The chief factor is the reaction of the capillaries to thermal injury.

Subsequent to a burn the capillaries in the injured areas dilate. The circulation stagnates, and blood plasma escapes through these injured capillaries into the tissue spaces. If the burn involves a sufficient number of capillaries the patient dies of shock due to a loss of blood fluid so rapid that nothing can be done to replace it. Intravenous fluids merely wash out into the tissue spaces. This is true circulatory shock from the mechanical loss of fluids, as reported by Blalock.[2]

If the burn is of lesser degree, so that fluid balance can be maintained, the patient survives the immediate shock stage. The inflammatory reaction of the capillaries persists, with continued loss of blood fluid and stagnation of the circulation.

One may observe all the local and general signs of the inflammatory reaction. Locally there are redness, heat and edema. The systemic reaction comprises fever, malaise, vomiting, convulsions and the other "toxic" symptoms previously mentioned. In other words, the toxic manifestations of burns are merely the systemic effects of diffuse thermal inflammation.

The escape of fluid from the capillaries becomes generalized, extending first to the liver, lungs and other parenchymatous organs and finally to all parts of the body. Because of the obvious inspissation of the blood and the fever it is common practice to force fluids intravenously and by mouth. Burned patients are thirsty because of the fluid loss and will drink enormous quantities of water. This is especially true of children, and because of the difficulty of intravenous fluid therapy for these patients they are often encouraged to take large amounts of fluid by mouth, the idea being that fluids of all kinds are indicated and can do no harm under these conditions.

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Dr. W. D. Gatch approved this work and assisted in the preparation of the manuscript.

From the Research Division and the Department of Surgery, Indiana University Medical Center.

Treatment demonstrated in space 488 in the Scientific Exhibit at the Ninetieth Annual Session of the American Medical Association, St. Louis, May 15-19, 1939.

1. Davidson, E. C.: Tannic Acid in the Treatment of Burns, Surg., Gynec. & Obst. **41**: 202 (Aug.) 1925.
2. Blalock, Alfred: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, Arch. Surg. **22**: 610 (April) 1931.

It is now known, however, that this reasoning is fallacious. When these patients are encouraged to take large quantities of water by mouth the burn shock is thereby complicated by a waterlogging of blood and tissues and by a metabolic disturbance which, for want of a better term, we have called water intoxication.

### WATER INTOXICATION

Before discussing further the relation of water to burn shock it may be well to review briefly the subject of water intoxication as reported under other conditions. The subject was first introduced by Rowntree [3] in 1923. He had noticed a peculiar symptom complex in several patients with diabetes insipidus who continued to drink their customary large quantities of water after urinary output had been sharply reduced by solution of posterior pituitary. Rowntree then gave large quantities of distilled water to animals by mouth and observed a syndrome which he called water intoxication, characterized by progressive asthenia, muscular twitchings, convulsions, coma and death. The chief pathologic feature observed to be present was cerebral edema accompanied by a sharp reduction in the serum chlorides.

Fig. 1 (case 1).—A girl aged 2 years who suffered a hot water scald resting comfortably eighteen hours after treatment by the tannic acid-silver nitrate method of Bettman. On the fourth day she died in convulsions.

Because of the fact that enormous amounts of water are necessary to produce alarming symptoms under ordinary conditions, little or no practical importance was attached to Rowntree's observations. Later, however, it was recognized that the so-called heat cramps of engine room and furnace workers are produced by drinking large amounts of water following excessive loss of chloride in perspiration. This condition may be prevented or relieved by proper salt intake. This same mechanism is responsible, in part at least, for the condition known as heat exhaustion.

Interest in the subject of water intoxication was again aroused in 1935, when Helwig, Schutz and Curry [4] reported a fatal case. In this instance a woman aged 50 died in convulsions thirty hours after a simple cholecystectomy. She had received by proctoclysis 9,000 cc. of water in the thirty hours.

### WATER INTOXICATION IN RELATION TO BURN SHOCK

Proceeding from these introductory remarks we are now ready to present the evidence which has given us a new conception of burn shock and the blood chemical disturbances related thereto. The thought that water intoxication may sometimes complicate burn shock came to us as the result of observations made in the following case:

CASE 1.—A girl aged 2 years was admitted to St. Vincent's Hospital, Indianapolis, on March 6, 1937, within an hour after she had fallen backward into a tub of hot water. The child was taken to the surgery and, under suitable narcosis, she was cleansed and her burns were treated by the tannic acid-silver nitrate method of Bettman.[5] Two hours after her burn she was completely tanned and comfortable in bed. The thin black membrane constituted what seemed to be an excellent dressing for her burn, as shown in figure 1.

It was apparent that the burns were superficial, but they were so extensive that a grave prognosis was given. The subsequent treatment was that which is prescribed in modern textbooks of surgery: namely, the forcing of fluids, the giving of large quantities of fruit juices, alkalis and calcium by mouth, and the intravenous administration of physiologic solution of sodium chloride and dextrose. The question of blood transfusion was discussed, but no blood was given.

Under this management the patient's condition seemed good for forty-eight hours. She asked for and was encouraged to take large quantities of fluids by mouth. Physiologic solution of sodium chloride and dextrose were given intravenously in moderate amounts. Though her condition seemed good, her burned areas became edematous on the second day.

On the third day the child became stuporous but could be aroused and would take large amounts of water and fruit juice. Rapidly a generalized edema developed, and at the end of seventy-two hours she went into convulsions and remained unconscious until her death six hours later, during which time her generalized edema continued to increase. Blood drawn near the time of death showed profuse hemolysis of red cells, practically no clot formation and a blood chloride reading of 140 mg. per hundred cubic centimeters—a figure so amazingly low that the determination was rechecked.

Necropsy performed promptly after death revealed a tremendous waterlogging of all tissues with quantities of free fluid in the abdomen and chest cavities. The liver was greatly swollen, pale and hard. The heart was firm and contracted; the lungs were moist but showed no consolidation. There were petechial hemorrhages in the mucosa of the pyloric antrum of the stomach and the duodenum. Kidneys and other viscera showed little gross change. The brain was not examined, but it is logical to assume that it was involved in the generalized edema. Smear and cultures of the heart's blood were negative for bacteria. Microscopic examination of tissues revealed edema and cloudy swelling, most apparent in the liver, which showed extreme parenchymatous damage. There was necrosis of the splenic corpuscles in varying degrees of severity. The kidneys showed cloudy swelling and parenchymatous degeneration. The corium of the superficially burned skin showed edema and capillary engorgement but no other evidence of infection.

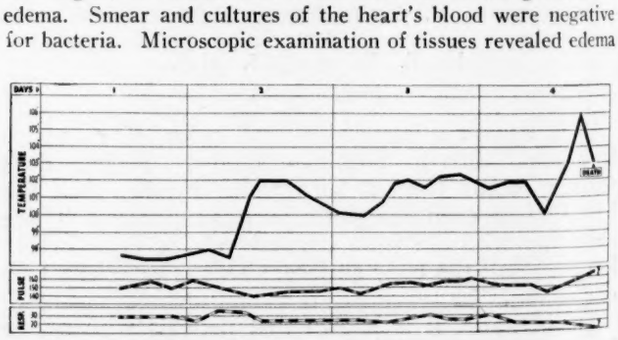


Fig. 2 (case 1).—Temperature chart.

This clinical picture obviously presents a far more profound disturbance than the water intoxication syndrome described by Rowntree. For want of a better term, however, we feel justified in assuming that this may be water intoxication superimposed on burn shock.

3. Rowntree, L. G.: Water Intoxication, Arch. Int. Med. **32**: 157 (Aug.) 1923.
4. Helwig, F. C.; Schutz, C. B., and Curry, D. E.: Water Intoxication, J. A. M. A. **104**: 1569 (May 4) 1935.
5. Bettman, A. G.: Tannic Acid and Silver Nitrate in Burns, Surg., Gynec. & Obst. **62**: 458 (Feb., No. 2A) 1936.

In this case, unfortunately, blood chemical studies were incomplete. However, the extremely low terminal blood chloride level and the massive waterlogging of all tissues are positive observations of great significance.

The laking of the red blood cells is evidence of a profound disturbance in osmotic relations. The failure of the blood to clot suggests a decrease in fibrinogen associated with a great dilution of blood proteins. Also, we are inclined to postulate that the convulsions which preceded this baby's death should be ascribed to water intoxication.

## EXPERIMENTAL STUDIES

This rather startling hypothesis led us to a series of studies on experimental animals (dogs). The animals were carefully selected for uniformity. They were clipped free of hair to the neck and were washed clean. Blood was drawn for determination of normal values. In order to produce definitely controlled burns, the animals were given morphine and a light ether anesthetic and immersed in water to the shoulders, the degree of burn depending on the temperature of the water and the time of immersion. After this they were kept comfortable and free from pain by adequate narcosis and careful attendance.

These animals were observed in series of five. Each member of a series received a different type of management, as follows:

(*a*) No fluids given.

(*b*) Water forced by stomach tube.

(*c*) Physiologic solution of sodium chloride and dextrose administered intravenously in large amounts.

(*d*) Acacia given intravenously in addition to solution of sodium chloride and dextrose.

(*e*) Transfusions of blood given twice a day in addition to salt solution and dextrose.

The following observations were made:

1. When the burns were relatively slight all animals tended to survive irrespective of treatment. There is one notable exception to this statement. An animal with a relatively slight burn can be killed by the persistent forcing of water by mouth. When liberal quantities of water are given by stomach tube to the animal with a mild degree of burn shock it is most likely to die in convulsions. The terminal blood picture is that of water intoxication. The control animal which is made comfortable by suitable narcosis takes little or nothing by mouth. It rests and very likely survives the shock state. Moderate amounts of salt and dextrose given intravenously are perhaps beneficial but are not essential to the recovery of animals with moderate degrees of burn shock. As previously stated, they tend to recover spontaneously unless large amounts of water are administered, in which case they die usually in convulsions.

2. When the burns were too severe all animals died in shock, commonly within twelve hours. In this group blood transfusions, given promptly and repeated frequently as the shock state progressed, tended to prolong life for many hours. Salt solution and dextrose given intravenously in the absence of blood transfusions were useless for the severely burned animals. The addition of acacia was of no benefit.

3. When the burns were of critical degree but not utterly hopeless in severity we made observations as follows:

(*a*) The control animals, to which no fluids were given, invariably died in shock, ordinarily within twelve hours.

(*b*) The animals which received large quantities of water by stomach tube tended to survive longer than the controls but always died, usually in convulsions.

(*c*) Salt solution and dextrose given intravenously in large quantities likewise tended to prolong life a few hours, during which time edema of the burned areas increased rapidly. Animals receiving this treatment died in shock regardless of the amount of fluid given.

(*d*) The addition of acacia to the intravenous solution was ineffective in saving life.

(*e*) The animals which received repeated large transfusions of blood in addition to salt and dextrose given intravenously were able to survive the otherwise fatal shock state. They became edematous but tended to maintain a normal blood chemical balance.

Numerous blood chemical observations were made. A detailed discussion of our experiments would be laborious and fortunately is unnecessary. We are including a few typical protocols which illustrate our observations under the stated conditions.

## BLOOD CHEMISTRY [6]

PROTOCOL 1 *(a).—Mild burn shock; recovery; no treatment.*

No. 364, weight 12.3 Kg. This animal was given morphine and a light ether anesthetic. It was then immersed to the shoulders in water at 60 C. for thirty seconds. The animal was given no treatment and survived the burn shock. There were no significant blood chemical changes at the end of fifty hours.

TABLE 1.—*Blood Chemistry, Protocol 1 (a)*

| | Normal | After 50 Hours |
|---|---|---|
| Hemoglobin, Gm. | 14 | 14.5 |
| Serum proteins, Gm. | 7.1 | 6.8 |
| Serum chlorides, mg. | 662 | 643 |
| Calcium, mg. | 10.4 | 11.5 |
| Sugar, mg. | 85 | 83 |
| Total nonprotein nitrogen, mg. | 30 | 29 |

PROTOCOL 1 *(b).—Mild burn shock. Death in forty-eight hours; water intoxication.*

No. 365, weight 13.2 Kg. In this experiment the procedure was the same as protocol 1 (*a*) except that large amounts of tap water were given by stomach tube. The first convulsion occurred after twenty-four hours. The animal died in coma forty-two hours after the burn, having received 7,000 cc. of tap water.

Note the sharp reduction in blood chlorides and the dilution of serum proteins. This was fatal water intoxication superimposed on the mild burn shock.

TABLE 2.—*Blood Chemistry, Protocol 1 (b)*

| | Normal | At Death |
|---|---|---|
| Hemoglobin, Gm. | 13 | 9.5 |
| Serum chlorides, mg. | 653 | 394 |
| Serum proteins, Gm. | 7.1 | 4.7 |
| Sugar, mg. | 99 | 56 |
| Total nonprotein nitrogen, mg. | 37 | 32 |
| Calcium, mg. | 11.5 | 9.5 |
| Potassium, mg. | 22 | 23 |

PROTOCOL 2.—*Fatal burn shock.*

No. 666, weight 20 Kg. This animal was given morphine and a light ether anesthetic. It was then immersed to the shoulders in water at 72 C. for three minutes. It was treated by seven transfusions of 400 cc. of whole blood, each combined with similar amounts of physiologic solution of sodium chloride with dextrose. Enormous edema developed, and death occurred at the end of forty-six hours.

Blood chemical observations at death revealed a sharp increase in hemoglobin and an elevation of total nonprotein nitrogen. It is significant that though large amounts of blood were given there was no increase in total serum protein. In other words it seems that blood plasma was lost into the tissues as rapidly as the blood transfusion replaced it. The change in the albumin-globulin ratio is significant.

6. The blood chemical figures in the tables are expressed as follows: Hemoglobin and serum proteins are determined as grams per hundred cubic centimeters; serum chlorides, serum calcium, blood sugar and total nonprotein nitrogen as milligrams per hundred cubic centimeters, and hematocrit value as per cent volume of the cells in 100 cc. of blood.

TABLE 3.—*Blood Chemistry, Protocol 2*

| | Normal | At Death |
|---|---|---|
| Red cell count, millions per cu. mm. | 7.83 | 8.40 |
| Hemoglobin, Gm. | 15.5 | 25 |
| Serum chlorides, mg. | 673 | 663 |
| Serum proteins, Gm. | 6.9 | 6.9 |
| Albumin, Gm. | 4.1 | 3.5 |
| Globulin, Gm. | 2.8 | 3.4 |
| Sugar, mg. | 114 | 125 |
| Calcium, mg. | 10.8 | 18.3 |
| Total nonprotein nitrogen, mg. | 30 | 98 |

PROTOCOL 3 *(a).—Critical shock; no treatment; death in eleven hours.*

No. 408, weight 18.8 Kg. This animal was given morphine and a light ether anesthetic. It was then immersed to the shoulders in water at 72 C. for one minute. No treatment was given. The animal died in shock eleven hours after the burn.

The blood chemical changes here were essentially the same as those observed in the animal described in protocol 2, which died in shock despite transfusion of enormous amounts of blood. There were an increase in hemoglobin and a sharp increase in the hematocrit percentage, indicating an actual loss in blood plasma. The chemical observations on the plasma which remained in the vessels showed little or no change.

TABLE 4.—*Blood Chemistry, Protocol 3 (a)*

| | Normal | At Death |
|---|---|---|
| Hematocrit, % | 45 | 62 |
| Hemoglobin, Gm. | 12.5 | 18 |
| Serum chlorides, mg. | 672 | 614 |
| Serum proteins, Gm. | 5.7 | 5.6 |
| Sugar, mg. | ..... | 105 |
| Calcium, mg. | 11.1 | 10.1 |

PROTOCOL 3 *(b).—Critical shock; water by stomach tube; death in sixty hours.*

No. 376, weight 17.5 Kg. This animal was given morphine and a light ether anesthetic. It was then immersed to the shoulders in water at 72 C. for one minute. It was given 7,000 cc. of tap water by stomach tube, much of which was vomited. Death ensued after sixty hours without convulsions.

The most significant blood chemical change noted here was the sharp fall in serum chlorides, the marked reduction of sugar and the terminal increase in nonprotein nitrogen. This is the picture of water intoxication superimposed on a critical state of shock.

TABLE 5.—*Blood Chemistry, Protocol 3 (b)*

| | Normal | At Death |
|---|---|---|
| Hemoglobin, Gm. | 13 | 13 |
| Serum proteins, Gm. | 7.2 | 6.5 |
| Serum chlorides, mg. | 672 | 374 |
| Calcium, mg. | 10.5 | 9.8 |
| Sugar, mg. | 128 | 26 |
| Total nonprotein nitrogen, mg. | 37 | 167 |

PROTOCOL 3 *(c).—Critical shock; physiologic solution of sodium chloride and dextrose given intravenously in large amounts; death in twenty-four hours.*

No. 546, weight 28.6 Kg. This animal was given morphine and a light ether anesthetic. It was then immersed to the shoulders in water at 72 C. for one minute. It was treated with 3,000 cc. of physiologic solution of sodium chloride with 5 per cent dextrose. Death ensued in twenty-four hours.

In this instance one notes the fall in the serum protein, reduction of blood sugar and terminal increase in total nonprotein nitrogen (discussed under blood chemical changes).

TABLE 6.—*Blood Chemistry, Protocol 3 (c)*

| | Normal | At Death |
|---|---|---|
| Hematocrit, % | 59 | 59 |
| Hemoglobin, Gm. | 16 | 16 |
| Serum chlorides, mg. | 725 | 774 |
| Serum proteins, Gm. | 7.2 | 5.4 |
| Sugar, mg. | 168 | 50 |
| Total nonprotein nitrogen, mg. | 26 | 82 |

PROTOCOL 3 *(d).—Critical shock; physiologic solution of sodium chloride and dextrose and 6 per cent acacia given intravenously in large amounts; death in fifty-six hours.*

No. 451, weight 15.19 Kg. This animal was given morphine and a light ether anesthetic. It was then immersed to the shoulders in water at 72 C. for one minute. It was given three intravenous injections during the next thirty-two hours, each consisting of 500 cc. of physiologic solution of sodium chloride containing 6 per cent acacia and 5 per cent dextrose. Death occurred twenty-four hours after the last injection as blood was being drawn for studies on blood chemistry. There were marked prolongation of bleeding and clotting time and hemolysis of the blood.

This experiment revealed the most marked changes in blood chemistry. Note the sharp reduction of hemoglobin, the fall in the hematocrit value, the fall in the serum proteins and the reduction in blood sugar (discussed on blood chemical changes).

TABLE 7.—*Blood Chemistry, Protocol 3 (d)*

| | Normal | At Death |
|---|---|---|
| Hemoglobin, Gm. | 15 | 7.5 |
| Hematocrit, % | 45 | 23 |
| Serum proteins, Gm. | 7.6 | 3.2 |
| Calcium, mg. | 10.5 | 13.2 |
| Sugar, mg. | 215 | 61 |
| Total nonprotein nitrogen, mg. | 26 | Unsatisfactory |

PROTOCOL 3 *(e).—Critical shock; repeated blood transfusions; recovery.*

No. 537, weight 19.5 Kg., given morphine and a light ether anesthetic. It was then immersed in water at 72 C. for one minute. This animal was given repeated transfusions, 300 cc. of whole blood plus 300 cc. of 10 per cent dextrose being administered in physiologic solution of sodium chloride. Three such intravenous injections were given the first day and one each day thereafter. The animal was killed after one week.

This subject survived the burn shock. It should be noted that blood chemical values at the time the animal was killed were essentially normal.

TABLE 8.—*Blood Chemistry, Protocol 3 (e)*

| | Normal | At Death |
|---|---|---|
| Hematocrit, % | 46 | 49 |
| Hemoglobin, Gm. | 13 | 15 |
| Serum chlorides, mg. | 666 | 725 |
| Serum proteins, Gm. | 7.1 | 6.0 |
| Sugar, mg. | 78 | 80 |
| Total nonprotein nitrogen, mg. | 32 | 57 |
| Calcium, mg. | 9.6 | 9.0 |

## BLOOD CHEMICAL CHANGES

The first point that we wish to emphasize is the variation in the blood picture, which depends on the degree of shock and the manner in which fluids are administered. Unless these factors are taken into account, the blood chemical values of shock have little or no significance. The physical mechanism of the shock state is obviously complicated. There are, however, two morbid phenomena which are definite: (1) circulation is stagnating and (2) blood fluids are escaping from the capillaries. This situation produces progressive degrees of blood concentration.

If no fluids are given, the blood chemical changes noted at death are those of blood concentration, as reported by Osterberg [7] and by Underhill and others.[8] When fluids are forced over several days' time, however, the blood chemical picture is different. The continued forcing of fluids by mouth can result in a condition of "water intoxication," which is apparent in the blood chemical picture at death. The continued intravenous administration of salt solution merely adds salt. Neither of these fluids will support life, nor will they stay in the capillaries.

When the shock state progresses rapidly, the change in chemical composition is often so slight that there may be no apparent explanation for the death of the animal. Note protocol 3 (*c*); critical shock terminated fatally in twenty-four hours, during which time 3,000 cc. of saline solution and dextrose was given to an animal weighing 28 Kg. The chemical changes as shown in the table seem insignificant at first thought. However there was

7. Osterberg, A. E.: Symposium on Acute Burns: Biochemical Studies, Proc. Staff Meet., Mayo Clin. **8**: 121 (Feb. 22) 1933.

8. Underhill, F. P.; Carrington, G. L.; Kapsinow, Robert; Pack, G. T., and others: Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, Arch. Int. Med. **32**: 31 (July) 1923.

a fall in serum proteins (7.2 to 5.4 Gm.) which took place in twenty-four hours and indicated severe capillary damage with rapid washing of blood fluids into the tissue spaces. This phenomenon must of necessity cause gross disturbances in the osmotic relations of the blood and tissues. A more complete discussion of this subject will be taken up in a later publication.

The inclusion of acacia in the intravenous fluid, as shown in protocol 3 (*d*), gave the most bizarre chemical picture we have observed. It appears that acacia tends to maintain the osmotic pull of the blood for a sufficient length of time to permit extreme watery dilution as a result of the continued forcing of fluids in the presence of progressive capillary leakage.

Our studies indicate that repeated transfusions of blood offer the only safe means of maintaining the blood chemical balance in the shock state. There is also an indication that blood plasma alone should be given, as the red blood cells become excessive in number. When the blood fluid balance is safeguarded in this manner other fluids may be given in moderate amounts.

The frequent observation of low blood sugar values we are not yet able to explain. It impresses us, however, that this point should be considered in the treatment of burn shock.

While these experimental studies were in progress we were called on to treat an extensive burn at the Methodist Hospital in Indianapolis. There follows a report of this most unusual clinical experience

CASE 2.—A girl aged 15 was badly burned on April 23, 1938, when her evening dress caught fire from a lighted match thrown on a ballroom floor. She was admitted to the hospital shortly thereafter, at 10:30 p. m. She was given morphine, and the charred remnants of her dress were removed. This revealed extensive burns of first, second and third degree, involving

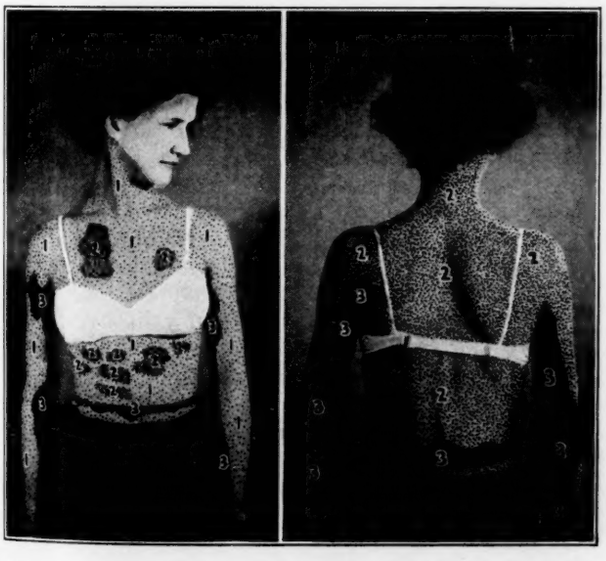

Fig. 3 (case 2).—A girl aged 15 years who on April 23, 1938, suffered an extensive flame burn, as shown by the stippling on the photographs taken one year later. Areas of first, second and third degree burn are indicated by the density of the stipple. Calculating by the method of Berkow,[10] we have estimated the burn to cover 55 per cent of the body surface.

hands, arms, neck, chest, abdomen and back, as indicated in figure 3. Her face was not injured. The deepest burns involved her arms, with which she had protected her face.

After sufficient narcosis she was placed in a tub of 1 per cent salt water at body temperature and given a bath with the aid of green soap. The duration of the bath was one and a half hours. Three hours from the time of the accident she was clean and comfortable in bed with sterile sheets and dressings moistened with saline solution. Her general condition was good, but the large size of her burn gave a bad prognosis.

Our first concern was the proper balancing of her fluid intake. Blood donors were typed at once. She was given 500 cc. of physiologic solution of sodium chloride containing

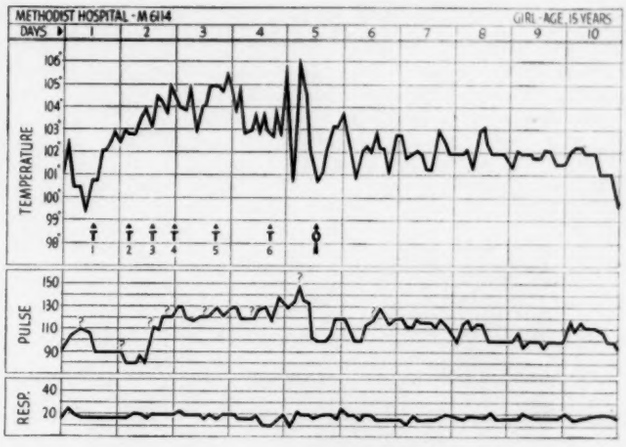


Fig. 4 (case 2).—Temperature chart. Small black triangles indicate blood transfusions. In the fourth and sixth, citrated blood plasma was given. The arrow indicates the beginning of five days in an oxygen tent. The question marks on the pulse curve are explained in the report of the case.

5 per cent dextrose. Fluids by mouth were limited. She was to have a total fluid intake of not more than 3,000 cc. in twenty-four hours. Of this, approximately 1,000 cc. was to be given by mouth as liquid diet, chiefly orange juice containing dextrose, and water administered frequently in small amounts. In addition she was given calcium gluconate at frequent intervals. For her thirst she was permitted to rinse her mouth and throat as often as she desired with cool water. The remaining 2,000 cc. of fluid intake was to be administered intravenously in the form of citrated blood, physiologic solution of sodium chloride and dextrose.

The first blood transfusion was given at the end of eight hours. At this time the patient's condition was good. Her pulse, however, was soft and difficult to count with certainty. She received 500 cc. of citrated blood with 500 cc. of physiologic solution of sodium chloride. Sixteen hours later her pulse again was uncertain, and the circulation was stagnating in the burned areas. With administration of another large transfusion of blood followed by salt solution and dextrose her circulation again improved. In this manner a total of six large transfusions were given in the first four days. On each occasion additional fluids were given in the form of physiologic solution of sodium chloride, dextrose and other agents to be mentioned later. At the time of each transfusion blood was drawn for chemical study.

The urine output was never reduced to zero but definitely lagged behind the fluid intake. Daily analysis of the scanty urine showed few signs of kidney damage. The clinical course, however, was painfully stormy and difficult to control.

A few hours after her third blood transfusion the girl's condition was not good. She was flushed and plethoric, and her circulation continued to stagnate. The burned areas were progressively more edematous. Her skin was dry and hot with a temperature ranging above 104 F. There was no sign of perspiration.

The hematocrit reading was 56 per cent, the red blood count was 6,000,000 cells with 18 Gm. of hemoglobin, and the total blood proteins were 4.6 per cent.

It was this situation which suggested to us the advisability of discarding the red blood cells from the next transfusion, with the thought that blood plasma alone would best safeguard

10. Berkow, S. G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, Arch. Surg. **8**: 138 (Jan.) 1924.

the fluid balance. A large amount of citrated blood was drawn and 350 cc. of blood plasma was obtained by centrifuging under sterile conditions.[9] On April 25, forty-eight hours after the burn, this citrated blood plasma was given intravenously and in addition 600 cc. of physiologic solution of sodium chloride containing dextrose and 100 cc. containing 50 per cent sucrose, a total of approximately 1,100 cc. of fluid, which constituted the fourth transfusion. After this the patient's condition was much improved, and the edema appeared to be lessened. Her temperature, however, was difficult to control. Sudden rapid rises made us fearful of a fatal hyperpyrexia. Tepid sponging of the dry skin caused chilling with no reduction of temperature. Only by means of cool retention enemas and repeated colonic irrigations of cold physiologic solution of sodium chloride were we able to keep her temperature below 106 F.

She was able to rest only with the aid of morphine given hypodermically in one-quarter grain (0.016 Gm.) doses alternating with pentobarbital sodium 1½ grains (0.1 Gm.) by mouth at frequent intervals.

Fig. 5 (case 2).—The girl on Oct. 6, 1939.

Eighteen hours from the time of the fourth transfusion the girl's circulation again was stagnating, but she was conscious and alert. Any manipulation caused chilling. Her temperature was persistently high and difficult to control.

With considerable apprehension another large transfusion of citrated blood was given, followed by additional fluids as before. Circulatory stasis improved, but the edema now increased rapidly and began to involve the face and other unburned areas. The patient was showing a tendency to intravenous reaction, and for this reason further effort in intravenous therapy was postponed as long as possible. Another large amount of citrated blood was drawn, however, and placed in the refrigerator in preparation for another transfusion of plasma.

For twenty-four hours the girl was closely watched until it became evident that all the symptoms just described were increasing. Her breathing was labored, and she was flushed and stuporous. The plasma carbon dioxide was 49 per cent and the total serum protein 4.2 per cent, with a hematocrit reading above 60 per cent.

Increasing edema was accompanied by progressive stasis of capillary circulation. To combat this situation the sixth transfusion was given. At 8 p. m. on April 27, four days after the burn, the patient received 350 cc. of blood plasma followed by 1,150 cc. of physiologic solution of sodium chloride containing 50 Gm. of dextrose and 1 ampule of Hartmann's solution, the latter being included because of the acidosis. This transfusion, though carefully given, was followed by a chill and rapid rise of temperature, as indicated in figure 4. With a cool colonic irrigation the temperature fell.

Three hours later there was another rapid rise of temperature, to a point above 106 F. The patient became delirious for the first time and then comatose and cyanotic, with pulmonary edema. All who saw her were convinced that she would die. A few hours later she awoke rational. She was very weak, cyanotic and dyspneic. Her pulse was fast and thready. An oxygen tent was placed over her, and the condition slowly improved.

Though she remained in a critical state for several more days there was one reassuring sign. Immediately after the last plasma transfusion the edema rapidly decreased and there was a sharp increase in urinary excretion. After five days in the oxygen tent with hypodermic administration of coramine, digitalis and other symptomatic drugs, the girl's color was good and circulatory tone was restored.

It is impossible to relate all the details of symptomatic management, nursing care and the local treatment of the burned areas. Because of the distribution of her burns the patient was unable to turn or move unassisted. A special bed was constructed to permit continuous wet dressing and frequent irrigation to her burned back, on which she had to lie. During the five days in the oxygen tent an ulcer developed on the cornea of the left eye, a distressing complication. For the management of this Dr. E. W. Dyar was responsible.

One month from the time of her burn the girl was taken home. All of her large burn was healed with the exception of several granulating areas on her arms, where the burns were deep third degree. On June 1 she returned to the hospital for three days, and her granulating areas were covered with Thiersch grafts. Two months from the time of receiving her burns she was completely healed. She has remained in good health and shows no sign of constitutional impairment.

Throughout the acute burn shock reaction this case was carefully studied. At no time did the systolic blood pressure fall below 80 mm. of mercury. At no time was the patient pulseless, although many times we could not be certain of the actual pulse rate. At these times transfusions of blood or blood plasma together with the intravenous fluids were administered. At no time was there complete anuria. During the period of her greatest edema, however, the urine output lagged far behind the fluid intake. A complete tabulation of laboratory data would be laborious and is unnecessary. With the exception of the abnormal values previously mentioned in the report, the numerous blood chemical and other laboratory reports give little or no indication of the stormy clinical course.

It is evident that this girl was in a grave state of burn shock for five days. We believe that a state of irreversible shock was prevented and that her life was saved by the repeated intravenous administration of properly balanced fluids, the most important components of which were blood and blood plasma.

Other significant therapeutic measures were the administration of oxygen, the control of temperature, proper sedation and the local treatment of her burns with mild antiseptic wet dressings and the scarlet red ointment preparation of Bettman.[5] At no time did sepsis complicate her recovery.

## COMMENT

Extensive burns present extremely complex problems in management. In this report we have related two cases, in addition to experimental observations, which

9. Drs. K. E. Thornberg, R. G. Fry and Horace Banks, pathologist, Methodist Hospital, prepared the citrated blood plasma.

have given us a new conception of the burn shock reaction. Our views, furthermore, are substantiated by numerous less complete clinical and experimental studies carried on by one of us (H. M. T.) over a period of ten years.

We are convinced that the successful treatment of burn shock depends on systemic measures and that the local treatment has little or nothing to do with this phase of the problem. There is no reason to believe that the local application of tannic acid or any other agent to the burned area is effective in preventing burn shock or in protecting the fluid balance of the body. It is unfortunate that for so many years this thought has confounded the essential requirements for burn shock therapy. Case 1 of this report shows an excellent example of this fallacy. In this instance a sterile tanned membrane was applied within two hours of the burn under ideal conditions. The patient died in convulsions on the third day.

Case 1 demonstrates in dramatic fashion what may happen to the blood chemistry when improperly balanced fluids are forced into a patient who is in a state of inflammatory shock due to an extensive burn. This baby received excessive amounts of fluids, chiefly in the form of water by mouth. The amazingly low blood chloride reading at death indicates to us a condition of water intoxication complicating burn shock. Our experimental studies substantiate this view.

We wish to emphasize the fact that the blood chemical values and the clinical course of patients in burn shock depend chiefly on the manner in which fluids are administered. Maintenance of fluid balance under such conditions presents a problem entirely different from that of the relatively simple fluid therapy required for patients who are merely dehydrated. The difference lies in the fact that burn shock results from a mechanism which causes stagnation of the circulating blood and a rapid loss of blood fluid through capillaries which are leaking into the tissue spaces. Under these conditions the forced administration of fluids is futile or even dangerous unless the blood chemical relationships are protected by repeated transfusions of blood or blood plasma.

As to prognosis and treatment, burns can be classified in three groups:

1. Relatively slight burns, in which shock is not a problem. The normal mechanisms of fluid and chemical balance may protect the patients sufficiently to permit recovery under any plan of systemic treatment or with no treatment at all.

2. Hopelessly extensive burns, in which no treatment will succeed in saving the lives of the patients.

3. Burns of critical degree, with the outcome depending greatly on the treatment; in these cases life may actually be saved by a rational therapeutic regimen.

Case 2, we believe, is an example of the third group. In the fourth and sixth transfusions blood plasma was given with beneficial results, as previously discussed. It is interesting to note that the girl's total blood protein fell as low as 4.2 per cent, even though repeated transfusions were given. There was also a persistent acidosis; in addition the heat-regulating mechanism was profoundly disturbed, with absence of perspiration and hyperpyrexia. The patient's recovery may be explained by the fact that the fluid balance and blood chemical relationships were maintained sufficiently near normal to sustain life throughout the self-limited period of the acute burn shock reaction. The importance of oxygen therapy should be emphasized.

It is important that burn shock be anticipated and treated by complete control of all phases of the case and by the administration of properly balanced fluids from the beginning. Any therapeutic effort is futile when once the shock state becomes irreversible.

The local treatment of large burns should be instituted entirely with the thought of preventing infection and providing for rapid healing. The importance of this is obvious, but further discussion of our views on local treatment does not come within the scope of this publication.

There are variable factors in the burn shock reaction which at present are somewhat obscure. The question of burn toxins we are not discussing at this time except to emphasize that the mechanism of death in so-called burn toxemia is secondary circulatory shock due to diffuse inflammation.

## SUMMARY

1. The tannic acid theory of the treatment of burns is fallacious. There is no local application that can be expected to save life after a large burn.

2. The first cause of death due to the extensive burn is shock. There are two phases in the burn shock reaction.

(*a*) The traumatic phase: Circulatory shock due to vascular stasis and the loss of blood plasma, which escapes into the tissue through capillaries injured by heat. Very large burns may be rapidly fatal by this mechanism.

(*b*) The inflammatory phase: A complex syndrome in which the loss of fluid is accompanied by the other morbid processes of diffuse thermal inflammation. This accounts for the toxic manifestations.

3. The blood chemical changes of the shock state depend largely on the manner in which fluids are administered. The indiscriminate forcing of simple fluids into a burned patient is futile and may lead to profound disturbances in the physical-chemical relations of the blood.

The persistent forcing of water by mouth under these conditions may cause a fatal water intoxication.

4. The successful treatment of burn shock calls for a complex therapeutic regimen. Blood transfusions should be given early and repeated frequently throughout the self-limited period of the reaction. Other fluids should be given in moderate quantities. Large amounts of dextrose are indicated.

5. In case 2 of this report recovery followed the giving of six large blood transfusions in four days. Because of polycythemia, in the fourth and sixth transfusions citrated blood plasma was given. The importance of oxygen therapy should be emphasized.

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**Relief from Mosquito Bites.**—Mosquito bites, while perhaps never serious in themselves, may lead to blood poisoning through scratching with the fingernails in the attempt to relieve the irritation, which is often intense. To relieve this irritation any one of the following may be applied, viz.: ammonia, glycerin, alcohol or iodine. According to Howard the most satisfactory remedy known to him is the application of moist toilet soap. He also mentions touching the puncture with a lump of indigo as affording instant relief, or touching the parts with naphthaline moth balls.—Herms, William B.: Medical Entomology, New York, Macmillan Company, 1939.

# THE TREATMENT OF SYPHILIS WITH SOBISMINOL MASS GIVEN BY MOUTH

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The treatment of syphilis would undoubtedly be facilitated by the discovery of a bismuth preparation which is effective when taken by mouth. Proper antisyphilitic therapy, when the medication is given by injection, requires frequent visits to the physician over a long period of time. Many patients discontinue their treatment prematurely or receive it at very irregular intervals because of the inconvenience of these visits or because of the pain of intramuscular injection. If a suitable oral bismuth preparation were available the attendance could safely be reduced and the pain of intramuscular injection avoided. It would be possible to continue antisyphilitic therapy during periods when regular visits to the physician are not feasible or for patients who experience reactions to intramuscular therapy. Several bismuth preparations designed for oral administration have been tried without conspicuous success. In 1937 Hanzlik, Lehman and Richardson [1] introduced a product called sobisminol into the therapy of syphilis. This drug may be administered either orally or intramuscularly, and the purpose of the present paper is to report the clinical results obtained with sobisminol mass when given by mouth.

Sobisminol mass [2] is given in capsules, each containing 0.2 Gm. of sodium bismuthate, 0.4 Gm. of triisopropanolamine and 0.1 Gm. each of propylene glycol and ethyl alcohol. The bismuth content of each capsule is 0.15 Gm. Hanzlik and his staff [3] have shown that this product is readily absorbed from the gastrointestinal tract in experimental animals and also in man. They have demonstrated that it is well tolerated in doses sufficient to produce and maintain a urinary excretion equal to or greater than that usually obtained with intramuscular injections of bismuth. These observations, which were confirmed by Sollmann, Cole and Henderson,[4] indicate that sobisminol mass should be a potent antisyphilitic agent. The clinical effects of this preparation have been reported only with regard to disappearance of surface spirochetes and the healing of cutaneous lesions. In these respects it was highly satisfactory.

Syphilis is a chronic infectious disease in which the prognosis without treatment is practically unknown but which often remains entirely asymptomatic throughout life. Since the final criterion of the effectiveness of any therapeutic agent is the ultimate clinical outcome, it is impossible to evaluate any antisyphilitic drug completely without an observation period of many years. We are therefore forced to rely on less adequate criteria. However, these do become of greater value with a longer period of observation. Sobisminol mass has been used in the syphilis clinic of the Stanford University Medical School for the last three years. During this time we have been able to evaluate in some respects the therapeutic effect of this preparation, but we do not feel that we have finally assessed its true worth.

There were 143 patients whose records were complete enough to be of use in the evaluation of sobisminol mass. In an additional forty-nine patients only data on tolerance were obtained. Each patient attended the clinic at intervals of one or two weeks, at which time he was carefully questioned as to tolerance and the clinical response was noted. Every effort was made to determine at each visit the exact number of capsules ingested during the preceding interval from the patient's story and the number of capsules dispensed. The daily dose estimated in this way is much nearer to the amount actually ingested than the prescribed dose would be. In this report the estimated dose will be used unless the prescribed dose is specified.

TABLE 1.—*The Concentration of Bismuth in the Urine with Various Doses of Sobisminol Mass When Determinations on Separate Single Specimens Are Averaged*

| Sobisminol Mass Ingested (Grams per Day) | Mean Excretion (Milligrams per Liter) |
|---|---|
| 0.26 to 0.75 | 3.1 |
| 0.76 to 1.25 | 2.6 |
| 1.26 to 1.75 | 3.2 |

It would be desirable to have another more objective method of determining the amount of sobisminol mass taken, and measurement of the amount of bismuth excreted in the urine has been suggested for this purpose. Such determinations should be done on the total urinary output, but this is not feasible in ambulatory patients who make only occasional visits to the doctor. It is therefore necessary to rely on single specimens in the hope that the concentration of bismuth in these may parallel the total excretion and indicate the amount of sobisminol mass ingested. Hanzlik [5] and Sollmann [4] and their co-workers demonstrated an increase in the average amount excreted with higher doses, but both observed wide daily variations.

All our patients were requested to leave specimens of urine for bismuth analysis on every visit to the clinic. The bismuth determinations were carried out in the department of pharmacology by Dr. A. J. Lehman and Dr. Walton Van Winkle Jr., first by a long quantitative method [6] and later by a shorter clinical method.[7]

The concentration of bismuth in single specimens of urine ranged between 0 and 24 mg. per liter. Individual observations varied widely in different patients and also

From the Division of Dermatology and Syphilology of Stanford University School of Medicine.

1. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sodium Bismuthate Soluble, Am. J. Syph., Gonorr. & Ven. Dis. **21**: 1 (Jan.) 1937.

2. The sobisminol mass used in this study was supplied by the Cutter Laboratories, Berkeley, Calif.

3. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, Walton, Jr.: Gastrointestinal Administration of Sobisminol: Absorption, Distribution and Excretion of Bismuth, J. Pharmacol. & Exper. Therap. **62**: 54 (Jan.) 1938. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sobisminol: Toxicity, Tolerance and Irritation According to Different Channels of Administration, ibid. **62**: 372 (April) 1938. Hanzlik, P. J., and Lehman, A. J.: Continued Voluntary Drinking of Sobisminol: General Effects, ibid. **62**: 389 (April) 1938. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Excretion of Bismuth After Intramuscular Injection of Sobisminol: Experimental and Clinical Results, ibid. **62**: 404 (April) 1938. Hanzlik, Lehman and Richardson.[1] Hanzlik, Lehman, Richardson and Van Winkle.[5]

4. Sollmann, Torald; Cole, Harold; Henderson, Katherine, and others: Clinical Excretion of Bismuth, Arch. Dermat. & Syph. **37**: 993 (June) 1938.

5. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, Walton, Jr.: Clinical Excretion of Bismuth After Oral Administration of Sobisminol, Arch. Dermat. & Syph. **36**: 708 (Oct.) 1937.

6. Lehman, A. J.; Richardson, A. P., and Hanzlik, P. J.: Improved Procedures for Estimating Bismuth in Body Fluids and Tissues: J. Lab. & Clin. Med. **21**: 95 (Oct.) 1935.

7. Hanzlik, P. J.; Lehman, A. J., Richardson, A. P., and Van Winkle, Walton, Jr.: Rapid Clinical Method for Estimation of Bismuth in Urine, Arch. Dermat. & Syph. **36**: 725 (Oct.) 1937.

in repeated specimens from the same patient. Practically all patients submitted occasional specimens of urine entirely free of bismuth even though they were apparently taking sobisminol mass regularly. Bismuth determinations in single specimens of urine proved to be of no practical value in estimating the amount of sobisminol mass ingested, nor could they be relied on to detect whether or not the drug was being taken.

Since single specimens of urine seemed of no value, we have averaged the urinary bismuth concentrations when multiple observations were made on the same patient. There were 118 individuals with from five to seventy-five separate determinations, the total number being 2,442, an average of 21 per patient. The results are shown in table 1.

It is evident from table 1 that the concentration of bismuth in urine is of no value in determining whether or not sobisminol mass is being ingested. This, of course, has no bearing on the correlation between ingestion and excretion, which has been demonstrated by Hanzlik [5] and Sollmann,[4] since in our study only occasional single specimens of urine instead of the total output were utilized.

Bismuth determinations were done on thirty specimens of blood, practically all from patients on a prescribed dose of 1.8 Gm. a day. The bismuth content varied from 0 to 0.16 mg. per hundred cubic centimeters, but twenty-one of these specimens contained less than 0.01 mg. per hundred cubic centimeters. There was no apparent relation between the bismuth in the blood and the therapeutic effect.

During the early part of the study the prescribed dose of sobisminol mass was 0.6 Gm. a day (one capsule three times a day). This amount was well tolerated and it was increased later to 1.2 Gm. (two capsules three times a day) and 1.8 Gm. a day (three capsules three times a day). We believe that 0.6 Gm. is inadequate, although it was taken by too few patients for us to be sure. The optimal dose appears to be 1.2 Gm. a day. A larger quantity had no greater therapeutic effect and was not as well tolerated. Moreover, when a dose of 1.8 Gm. was prescribed this amount frequently was not taken. In more than one third of the patients given this dose the amount actually taken was less than 1.2 Gm. When 1.2 Gm. was prescribed, only one sixth of the patients took less than 1 Gm.

Sobisminol mass was well tolerated by almost all patients and no really serious reactions occurred. Thirty-seven per cent of 192 patients experienced some degree of reaction to the drug. Mild gastric disturbances were the commonest reactions, constituting 68 per cent of the total. These occurred most commonly during the first week and consisted of a feeling of fulness in the epigastrium or a sensation of hunger, occasionally accompanied by nausea and vomiting. Most patients noticed a slight increase in frequency of bowel movements but only 6 per cent actually had diarrhea. In five patients a bismuth line developed. Four others had an acute stomatitis which came on during the first few days of medication, disappeared rapidly following withdrawal of the drug and did not recur when it was resumed. An occasional patient after taking a capsule with insufficient water experienced a severe burning sensation in the esophagus that persisted for several days. A pityriasis rosea-like eruption, probably due to bismuth, occurred in three patients, and another had a toxic erythema for which no other cause could be found. Urinalyses were made at frequent intervals and in no case was there any suggestion of renal damage. Liver function tests were not done, but there was never any clinical evidence of hepatic damage. Sobisminol mass was discontinued in five cases on account of severe gastrointestinal reactions and in five more intramuscular bismuth was substituted because we were convinced that the drug was not being taken with any degree of regularity.

The tolerance of a drug having been established, its therapeutic efficiency must be investigated. The effect of an antisyphilitic agent may be appraised in a few days by the rapidity with which it causes spirochetes to disappear from surface lesions in early syphilis. It can be estimated within a few weeks by the rate of involution of benign tertiary and early cutaneous lesions. It may be measured over a period of months by the symptomatic response in late syphilis, but only by the ultimate outcome as determined over a period of many years can it be proved.

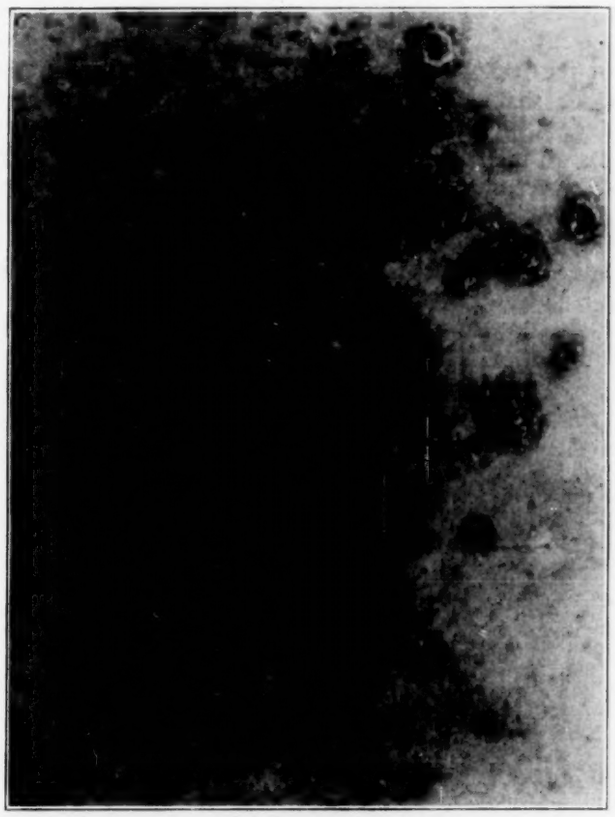


Fig. 1.—The appearance of lesions on the back in secondary syphilis Nov. 27, 1936.

The rapidity with which sobisminol mass caused Spirochaeta pallida to disappear from surface lesions was observed in thirty-three cases of seropositive primary or secondary syphilis in which neoarsphenamine was withheld for a period of two weeks. We did not feel justified in using sobisminol mass alone in seronegative primary syphilis, even for a brief period, because the prognosis is definitely better when treatment is started before the serologic reactions become positive. However, two patients failed to return for serologic reports and received only sobisminol mass for eight and ten days. The serums of both were then strongly positive. In the patients who were followed for dark field reversal, careful examinations were made on at least three prep-

arations each day. These examinations were continued in nearly every case until results of dark field examinations were negative on three successive days. No local medication was used. A few patients were given 0.6 or 1.2 Gm. of sobisminol mass daily, but 1.8 Gm. was prescribed for the majority and the average time required for the disappearance of Spirochaeta pallida was 4.2 days in twenty-nine cases. In the other four the result of dark field examination was still positive on the fourteenth day when neoarsphenamine was started.

The rate of involution of the lesions of early syphilis with sobisminol mass was observed in fifty-one cases. Fourteen were in the primary and thirty-seven in the secondary stage. Eleven primary lesions were completely involuted in from two to fourteen days, the average being 10.3 days. In each of the other three the involution was estimated at 90 per cent at the end of fourteen days. The secondary lesions in twenty-six cases were entirely healed in from four to fourteen days, with an average of 10.4 days. In eleven other cases the lesions had not completely healed at the end of fourteen days when neoarsphenamine was begun. At this time the average degree of involution was estimated as 70 per cent. An example of complete involution of psoriasiform secondary lesions after

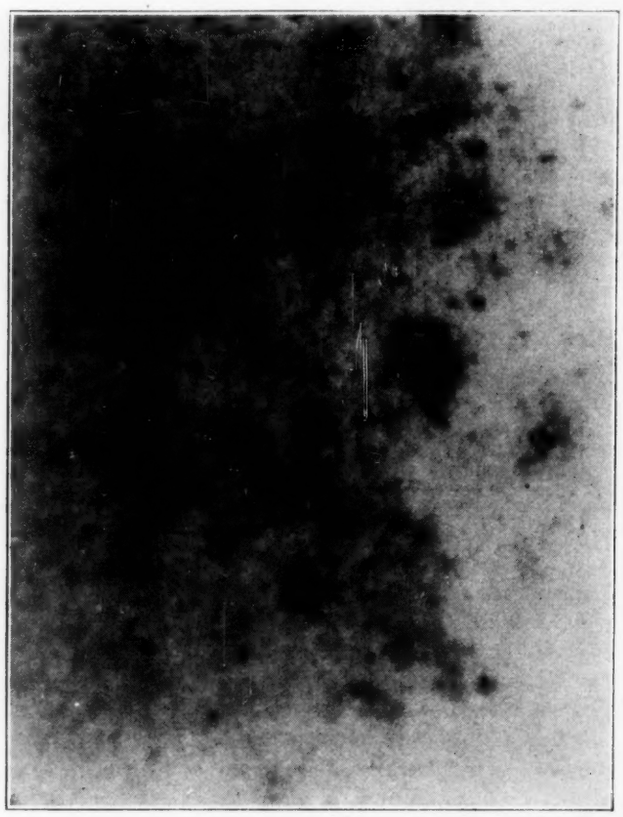


Fig. 2.—Appearance of lesions shown in figure 1 December 9, showing healing after treatment with sobisminol.

twelve days of sobisminol mass alone with an average dose of 1.65 Gm. daily is shown in figures 1 and 2. The residual pigmentation, evident in figure 2, often persists for months and was disregarded in determining involution.

The rate of involution of various types of late cutaneous lesions was determined in twenty-eight cases. Healing was complete in from one to twelve weeks, with an average of 4.4 weeks. Since the lesions were observed at weekly intervals, the true average is probably slightly less than this. The rate of disappearance was dependent on the amount of induration and destruction and consequently varied widely. On the whole, the response was extremely satisfactory. An example of involution in a deeply ulcerated gumma is shown in

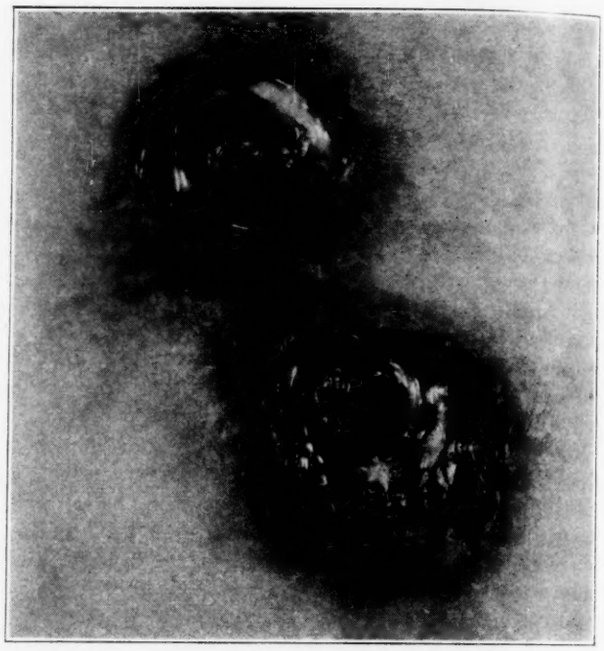


Fig. 3.—The appearance of lesions in tertiary syphilis, Oct. 15, 1936.

figures 3 and 4. At the time figure 4 was made the patient had taken an average of 1.75 Gm. of sobisminol mass daily for six weeks without other therapy.

A summary of the data on the rate of involution of lesions under sobisminol mass therapy is given in table 2.

About half of the patients were given 1.8 Gm. of sobisminol mass daily and the other half 1.2 Gm., with the exception of a very few who took 0.6 Gm. There was no discernible difference in the time of dark field reversal or of involution between any of these groups.

In seventy-three cases of late syphilis, including those presenting cutaneous lesions, treatment was initiated with sobisminol mass and was continued without other antisyphilitic therapy for an average period of 4.7 months. Twenty-three patients took it for more than six months and seven for more than one year. A serologic reversal occurred in three cases, in one at four months and in another at seven months. In the third the Wassermann reaction was two plus after ten months of sobisminol mass, at which time treatment was discontinued, and the Wassermann reaction was negative three months later.

In a number of patients with late syphilis of the cardiovascular or nervous system there seemed to be subjective improvement with sobisminol mass. However, when oral medication is used instead of intramuscular injection, about which patients are likely to be quite apprehensive, one hesitates to ascribe subjective improvement to the action of the drug.

In late syphilis the only indexes of therapeutic efficiency that can be obtained in a short time are the

involution of lesions, a Wassermann reversal and subjective improvement. Many years is required for the true evaluation of an antisyphilitic drug because of the extremely variable course of the disease, and the final effect of treatment can never be determined until death has occurred.

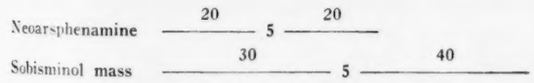
The final result in early syphilis is even more remote than in late, but certain clinical or serologic events may occur that will permit earlier evaluation of a drug. The most important of these events are Wassermann fastness, involvement of the central nervous system and serologic or clinical relapse. When these occur during treatment or after apparently adequate treatment, their frequency is a valuable index of the effectiveness of therapy.

When oral bismuth was first used, it was decided to follow the same plan of treatment for early syphilis then in effect in the clinic, except for the replacement of iodobismitol by injection with sobisminol mass by mouth. According to this plan, neoarsphenamine and iodobismitol were given simultaneously once a week for twenty weeks. Neoarsphenamine was then omitted for five weeks, after which a second course of twenty injections was given. The initial course of iodobismitol was

TABLE 2.—*The Rate of Involution of Syphilitic Lesions in Patients Treated with Sobisminol Mass*

| No. of Cases | Diagnosis | Involution Complete | Average Time for Involution | Per Cent Involution in Lesions Still Present at 14 Days |
|---|---|---|---|---|
| 11 | Primary | 1–14 days | 10.3 days | |
| 3 | Primary | | | 90% |
| 26 | Secondary | 4–14 days | 10.4 days | |
| 11 | Secondary | | | 70% |
| 28 | Tertiary | 1–12 weeks | 4.4 weeks | |

continued to thirty doses and a second course of forty doses was given after an interval of five weeks. The usual dose of neoarsphenamine was 0.45 Gm. for both men and women, and that of iodobismitol was 2 cc. In the present series, instead of weekly injections of iodobismitol, sobisminol mass was given by mouth in divided daily doses of 1.2 or 1.8 Gm. during corresponding periods. The only other deviation from the original plan was the two week period in which some of the patients received sobisminol mass alone, prior to the administration of neoarsphenamine. The scheme of treatment is shown here diagrammatically, in which the figures indicate the number of weeks.




Ninety-three patients with early syphilis were given this type of therapy. Thirty-six were in the primary stage, seventeen being seronegative. Fifty-four had secondary lesions and three were early latent. Thirty-nine of these patients were followed for more than a year, nineteen for more than eighteen months but only five for more than two years. The average total period of observation was eleven months. Seventy-four were followed for more than five months and the results in these may be compared to the results that were reported by Beckh and Barnett [8] in a similar series in which iodobismitol was administered.

There were only thirty-six patients who were initially seropositive and whose Wassermann reactions of the blood were repeated at five months, permitting comparison with the iodobismitol series. Thirty-one of these, or 86 per cent, became negative. This figure compares quite favorably with that obtained by similar treatment with iodobismitol, in which forty-six of fifty-eight, or 79 per cent, became negative.

TABLE 3.—*The Incidence of Serologic Reversal and of Cerebrospinal Fluid: Abnormalities Obtained with Sobisminol Mass Therapy in Comparison with That Obtained by Similar Treatment with Iodobismitol*

| | Type of Bismuth | |
|---|---|---|
| | Sobisminol Mass | Iodobismitol |
| Number of patients | 36 | 58 |
| Seronegative at 5 months | 31 (86%) | 46 (79%) |
| Number of patients | 51 | 43 |
| Positive cerebrospinal fluids | 2 (4%) | 7 (16%) |

The cerebrospinal fluid was examined at some time during the course of treatment in fifty-one cases. None of these showed any clinical evidence of involvement of the nervous system and only two had positive reactions of the spinal fluid. These were examined approximately six months after the beginning of treatment. Both showed a moderate pleocytosis and a slightly elevated protein content. The Wassermann reactions were positive with 1 cc. of fluid but negative with smaller quantities, and the colloidal gold curves were normal. In the series treated with iodobismitol, seven of forty-three spinal fluids gave positive reactions. These results indicate that sobisminol mass may prove to be of value in the prevention of neurosyphilis.

The incidence of serologic reversal and of cerebrospinal fluid abnormalities obtained with sobisminol mass

TABLE 4.—*The Incidence of Relapse in Early Syphilis in Patients Receiving Sobisminol Mass in Comparison with That of a Similar Group Receiving Iodobismitol*

| | Type of Bismuth | |
|---|---|---|
| | Sobisminol Mass | Iodobismitol |
| Number of patients | 74 | 80 |
| Relapses | 9 (12%) | 9 (11%) |
| Clinical | 8 | 4 |
| Serologic only | 1 | 5 |
| Average time of relapse | 14 months | 18 months |

therapy in comparison with that obtained by similar treatment with iodobismitol is summarized in table 3.

Even though the series is small, the figures in table 3 suggest that sobisminol mass is superior to iodobismitol in producing a Wassermann reversal and preventing involvement of the nervous system.

In the present series of seventy-four patients there were several who relapsed during treatment. The incidence of these relapses in comparison with that observed under similar treatment with iodobismitol is shown in table 4.

8. Beckh, Walter, and Barnett, C. W.: The Effect in Early Syphilis of Combined Treatment in Comparison with Alternating Treatment, Arch. Int. Med. **63**: 974 (May) 1939.

Of the patients who relapsed under sobisminol mass therapy, typical cutaneous secondary lesions developed in five. Two of these had recurrences of positive Wassermann reactions coincident with a relapse, and a third was Wassermann fast. No serologic data were obtained in the other two. A positive dark field examination was obtained in only one of these patients, but all lesions involuted promptly after modification of treatment and there can be little doubt as to the accuracy of the diagnosis. In the other three cases the relapse consisted of an acute iridocyclitis. In one there was a recurrence of a positive Wassermann reaction at the time of relapse. In the other two there may be some doubt as to the diagnosis of relapse, since in one no serologic reaction was obtained and in the other the Wassermann reaction remained negative.

From table 4 it appears that the incidence of relapse is approximately the same with the two types of therapy. If the two series differed only in the bismuth

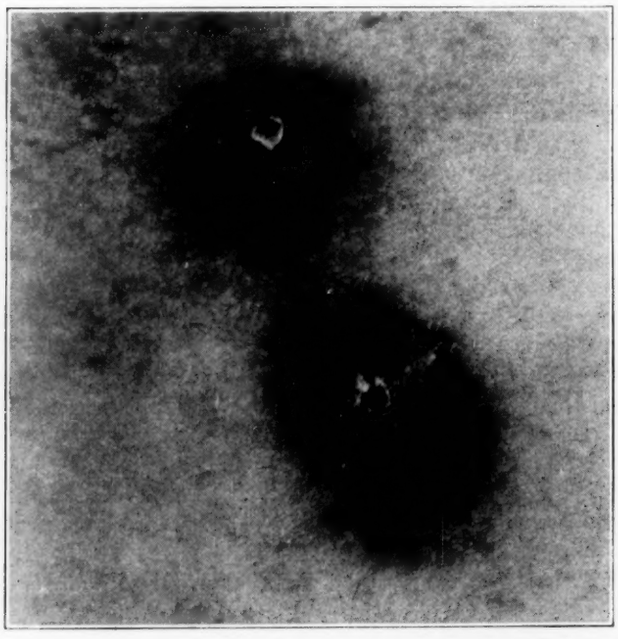


Fig. 4.—Appearance of lesions shown in figure 3 November 25, showing healing after treatment with sobisminol.

preparation used, this conclusion would be justified. There is, however, another important difference, namely the time of observation. It is improbable that many more relapses will occur in the iodobismitol group, since the majority of recurrences in early syphilis appear within two years after infection, and two years has elapsed since iodobismitol was replaced by sobisminol mass in this type of therapy. On the other hand the patients receiving sobisminol mass are still within the period of potential relapse and more clinical or serologic recurrences may be expected to appear in this group. When one considers that the average time of relapse after treatment was begun in the iodobismitol group was eighteen months and that the average total period of observation in the sobisminol mass series is only eleven months, such recurrences must be anticipated. Moreover, in the latter group only seventeen have been followed for as long as eighteen months, and of these two have already had a relapse. If the period of observation were longer, sobisminol mass would probably compare less favorably with iodobismitol in the prevention of relapse than is indicated in table 4.

In those patients who did have a relapse, an attempt was made to discover a possible explanation. Each patient was repeatedly questioned regarding the number of capsules taken, and this was checked with the amount dispensed. In no case could we prove that the drug was not being taken regularly. The excretion of bismuth in the urine was well within the average limits in every patient. There was no evident relationship between the incidence of relapse and the age, sex, diagnosis, regularity of treatment, amount of neoarsphenamine or dose of sobisminol mass. Except for the bismuth product itself, the only factor that seemed to be of importance in the production of relapse was the treatment pattern employed.

In the report of Beckh and Barnett,[8] it was shown that this combined type of treatment was productive of more relapses than a simple alternating type, even when the same bismuth preparation was used. Had we been aware of this at the time the present study was planned, sobisminol mass would have been used in alternating courses with neoarsphenamine. However, since the present treatment was identical with the combined type except for the substitution of sobisminol mass for iodobismitol, the probable higher incidence of relapse with sobisminol mass must be ascribed to the drug and not altogether to the type of therapy.

There are obvious disadvantages in the oral treatment of syphilis. When treatment is given by injection, the physician knows not only that the patient has received the medication but the amount injected and the time of administration. When it is given orally the control is entirely in the hands of the patient, and the physician has only his word that the drug is even being taken. This disadvantage of oral medication is important in the treatment of syphilis because prolonged and uninterrupted treatment is essential. Even intelligent and conscientious patients will often admit irregularities in ingestion after a few weeks or months. Although the great majority of patients prefer oral therapy, there are a few who have little discomfort after intramuscular injection and consider frequent oral medication a nuisance. There is also the danger that the release of an effective antisyphilitic drug which can be taken orally may lead to self medication.

In spite of the disadvantages, there is a definite place in the treatment of syphilis for an effective oral bismuth preparation such as sobisminol mass. Continuous treatment is essential in early syphilis and of considerable importance in late syphilis. Sobisminol mass provides a means of preserving continuity in treatment when regular visits to the physician are impossible or when severe reactions make intramuscular administration unpractical.

## SUMMARY

Sobisminol mass is well tolerated when taken by mouth in therapeutically effective doses. It produces rapid involution of lesions in early and benign late syphilis and causes the disappearance of spirochetes from the surface lesions of early syphilis. It appears to reduce the incidence of involvement of the nervous system but does not prevent a clinical or serologic relapse when substituted for intramuscular bismuth in the treatment of early syphilis. It is a valuable addition to antisyphilitic therapy and certainly deserves further clinical trial.

Clay and Webster streets.

# SOBISMINOL MASS: CLINICAL RESULTS WITH ORAL ADMINISTRATION

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This report represents the results of the first eighteen months of our experience in the clinical use of a bismuth preparation for oral administration (sobisminol mass),[1] which has been made available through the cooperation of Professor Hanzlik of Stanford University.[2] It was supplied in capsules containing the reaction product of sodium bismuthate 0.2 Gm., triisopropanolamine 0.4 Gm., propylene glycol 0.1 Gm. and ethyl alcohol 0.1 Gm. This represents approximately 150 mg. of elemental bismuth. We now report clinical results in ninety cases, including cases of seropositive primary, secondary, late benign (bone, skin, mucous membrane), central nervous system (tabetic, meningovascular) and congenital syphilis.

## GENERAL CONSIDERATIONS IN ORAL VERSUS INTRAMUSCULAR THERAPY

There are many obvious facts which make oral administration preferable to any other type as a therapeutic procedure, but with diseases such as syphilis, because of the nature of the drugs which must be used, certain singular problems arise which require special consideration.

One of the most important major objections to oral therapy with drugs whose absorption from the gastrointestinal tract is not complete and consistent is that, since the exact amount mobilized for the circulation and tissues is not determinable, oral administration is inaccurate and is dangerous from the standpoint both of overdosage and toxicity and, with syphilis, of the opposite danger, i. e. inadequate dosage, with its well known consequences. This objection is serious and valid and deserves careful consideration.

The same criterion, however, must be applied in examining bismuth preparations used by other routes. Intravenous administration of completely soluble drugs satisfies our requirements nicely, but, on the other hand, intravenous therapy has many fundamental dangers and it is well established that intravenous administration of bismuth raises the toxicity of the drug to such a point that its use is impossible.

Let us examine, then, the conventional intramuscular administration of bismuth from the standpoint of the criterion which we applied to the oral administration of drugs.

We find that, with the exception of a few of the highly soluble preparations, most of the preparations in common use leave varying quantities at the site of injection and that in some cases, because of local reactions and encapsulation or the formation of salts, the quantity may be large. We find then that, although we do know the exact amount of the drug introduced into the body, we do not know the exact amount actually mobilized in an active form. It is therefore possible to have gross underdosage with certain compounds for intramuscular administration and, in certain instances, the storage and accumulation of quantities of the drug which might under certain conditions result in serious intoxication. We find that our main objection to oral therapy with partially absorbable drugs applies equally strongly to partially absorbable drugs given into the muscle and that the depot type of treatment is far from the ideal pharmacologically.

It seems therefore that so far as accuracy is concerned (and for the present without regard for the peculiar requisites of the desirable drug in the treatment of syphilis) the drug which is completely tissue soluble is the drug of choice for intramuscular therapy and that a drug whose absorption from the gastrointestinal tract is consistent and quantitatively known is equally desirable for oral therapy.

If two such drugs were available and were shown to be equally effective in therapeutic activity, the choice would be determined by balancing the advantages and disadvantages inherent in the intramuscular route against those of the oral route. It is unnecessary to enumerate the objections to intramuscular injection, but it immediately becomes obvious that, all other things being equal, the oral route of administration is the desirable one.

## ROLE OF BISMUTH IN THE TREATMENT OF SYPHILIS

When one begins to consider the role of bismuth in the treatment of syphilis, certain factors appear which immediately make the problem of the choice of drug and the route of administration much more complex than was indicated in the previous section.

It has been generally considered that of all the attributes of the heavy metals the most important is their capacity to "build resistance" or stimulate the "defense mechanism." Thus far the knowledge of this phenomenon is meager and is best described as nebulous. Possibly a more concrete conception is to interpret this mechanism as one of "relapse prevention." Regardless of the fact that knowledge of the mechanism is slight, the observable fact remains that the important function of bismuth is not in killing spirochetes but in reenforcing the therapeutic attack in some way which makes the human organism better able to consolidate the gains brought about by the arsenical drugs. If it can be shown therefore that this effect of bismuth is altered by or in any way connected with the route of administration, it becomes apparent that the problem is not simply the question of getting a given amount of bismuth into the circulation.

One obvious question is immediately raised: Is the relapse-preventing effect of bismuth due to the fact that the depot in the muscle represents a long time supply of small quantities of previously unmobilized bismuth, or is the effect brought about by the bismuth which has been deposited in body tissues and fluids in combination with serum proteins? The answer to this question would be of greatest value in the solution of the bismuth problem. Excretion studies by many different investigators have shown that, almost regardless of the type of bismuth preparation given by muscle, approximately

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1. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sodium Bismuthate Soluble, Am. J. Syph., Gonor. & Ven. Dis. **21**: 1 (Jan.) 1937. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Clinical Excretion of Bismuth After Oral Administration of Sobisminol, Arch. Dermat. & Syph. **36**: 708 (Oct.) 1937; Gastrointestinal Administration of Sobisminol: Absorption, Distribution and Excretion of Bismuth, J. Pharmacol. & Exper. Therap. **62**: 54 (Jan.) 1938. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sobisminol: Toxicity, Tolerance and Irritation According to Different Channels of Administration, ibid. **62**: 372 (April) 1938. Hanzlik, P. J., and Lehman, A. J.: Continued Voluntary Drinking of Sobisminol, General Effects, ibid. **62**: 389 (April) 1938.

2. E. R. Squibb & Sons supplied the drug.

50 per cent of the drug administered is retained in the body after the initial period of appreciable excretion and that the retained portion is excreted in almost immeasurable quantities over a prolonged period. This seems to be true even of those highly absorbable drugs which are known to leave the injection depot almost completely within a very short period (days or weeks). During the period of appreciable excretion, therapeutic activity such as spirocheticidal effect is easily demonstrated. The period of prolonged minor excretion (many months) is the period about which little is known but which may be the crucial and significant one. In this period the bismuth is distributed to the tissues and tissue fluids and is present in minute quantities, and it is here that it may play its essential role of apparent stimulation of defense or resistance or act to prevent relapse.

It would seem therefore that this effect is due to the peculiar fact that bismuth tends to be remobilized and excreted very slowly from the tissues in which it has been distributed rather than to the fact that there is a long time depot supply. Assuming this to be acceptable it then seems that, so long as the bismuth is absorbed into the circulation and distributed to the tissues and tissue fluids in adequate amount, neither the type of preparation nor the route of administration is of fundamental importance.

The classic experiment of Kolle would suggest that such a conclusion is incorrect and that bismuth is effective only when freshly mobilized from a depot and exerts a spirochetostatic effect only so long as the depot remains in place. This would indicate that the bismuth in tissue and tissue fluid has no therapeutic effect. Levaditi is of the opposite opinion and supports the contention which we have outlined. In the meantime the question is not answered, so that we cannot make a choice on the basis of known pharmacodynamic facts.

We must turn therefore to clinical results and methods. These methods represent after all the ultimate answer to therapeutic questions but with syphilis require many years for a complete answer. In this particular situation it must require a minimum period of five years to show the ultimate therapeutic results attained by incorporating the several bismuth compounds into an otherwise similar treatment system, and only by careful study of the results of treatment can the final choice be made as to which type of bismuth is superior or whether all types are equally acceptable.

In the meantime the individual clinician must decide whether he wishes to accept new drugs and methods which show great promise but which are yet unproved, or to continue using drugs and methods which admittedly can be improved but which time has shown can produce a degree of therapeutic success.

### CLINICAL RESULTS OF ORAL ADMINISTRATION

Our first reaction to the use of bismuth by mouth was that, if it should prove equally effective therapeutically, the obvious advantages would make this method of treatment the one of choice. After our brief experience with this type of treatment we gained the following definite impressions:

Advantages:

1. The majority of patients prefer taking capsules by mouth three times a day to intramuscular injection once a week.
2. The drug can be used by persons who do not absorb bismuth from the muscle.
3. Apparently no depots are formed, and we did not find any evidence of cumulative toxic effects.
4. Management of a large number of patients in the clinic would be greatly facilitated and probably less expensive, since no apparatus for treatment is required.
5. Patients tend to be more regular in their treatment because many of them greatly fear the injection, with its attendant pain and discomfort.
6. Treatment accidents such as abscess and embolism are precluded.

Disadvantages:

1. The success of the treatment is directly dependent on the intelligence and cooperation of the patients, many of whom forget or neglect to take their capsules regularly because of various unimportant reasons.
2. A small number of patients are unable to tolerate treatment by mouth because of serious gastric intolerance.
3. There is a rather high incidence of gastrointestinal reaction which, although mild, tends to discourage patients during the early weeks of treatment.
4. Because of absence of depots, this method of treatment does not have any sustained effect, as shown by the fact that several patients with early involvement showed relapses within two weeks after treatment was discontinued.
5. The fundamental objection to all oral treatment holds true here, i. e. that the amount of the drug actually assimilated is not easily determined and apparently varies from day to day, depending on the functional state of the gastrointestinal tract.

Dosage: Early in this study we used nine capsules of sobisminol mass daily as a standard dose. This represented 1.25 Gm. of bismuth. Later on it was found that six capsules, or about 0.84 Gm. of bismuth, daily seemed to be just as effective therapeutically and to be somewhat better tolerated, and this was used as the standard dose thereafter.

### DESIDERATA FOR NEW BISMUTH COMPOUND

Keeping in mind that the prime criterion by which to judge a drug in the treatment of syphilis is the ultimate long time results, as suggested previously, but unable because of certain circumstances operating in this clinic to incorporate bismuth given orally into our treatment of early syphilis as the sole heavy metal, we have had to content ourselves with observing its effects in relation to the following points:

1. Does it reach the blood stream and tissues in active form in adequate amount? This was studied by observing the effects on active observable lesions of all types.
2. How well is it tolerated and what are its toxic effects?
3. Does it have a sustained optimum therapeutic effect? This we consider to be demonstrated by sustained effect for an appreciable period after the administration of the drug was discontinued.

We have considered that the circumstances under which we have studied the drug did not allow for a significant effect on serologic reactions and therefore do not include such effect in the report.

We have chosen to demonstrate question 1 in the following manner:

Patients with seropositive primary and with secondary syphilis were given sobisminol mass orally as the initial treatment, and this treatment was continued for two weeks without the addition of any other drug. At the end of two weeks, treatment with an arsenical was begun regardless of the state of involution of the active lesion, since it was felt that any further delay would jeopardize the prognosis. On the other hand, active late benign lesions of the bones, skin and mucous membrane were allowed to go for several months if possible to allow for complete involution. Certain elderly persons with late latent syphilis and late neurosyphilis (ade-

quately treated) have also been allowed to continue with the drug for many months. Evidence of activity of the drug was measured by the rate of involution of the lesions as compared with the natural involution and that achieved with other drugs. Patients with symptomatic late neurosyphilis were chosen also to show that the drug could bring about relief of symptoms. Although these results are not objective in any sense of the word, the conditions under which results were measured allow us certain conclusions, which will be discussed later.

Question 2, on toxicity and reactions, was studied with simple statistical analysis in the usual manner.

Question 3, on evidence of sustained effect, is difficult of evaluation and probably must be interpreted differently with early and with late syphilis. From the clinical standpoint we considered that relapse and reactivation during treatment or soon after its cessation were evidence of lack of sustained effect. It should be noted that so many factors enter into this situation that any conclusions drawn are subject to question.

## RESULTS OF TREATMENT

There were five cases of seropositive primary syphilis, twenty-seven cases of secondary syphilis (all types represented), twelve cases of late benign syphilis of the bones, skin and mucous membrane, twenty-three cases of syphilis of the central nervous system (mainly tabetic and meningovascular) and twenty-three cases of latent syphilis (early and late).

*Seropositive Primary Syphilis.*—The average period of involution was fourteen days, with extremes of ten and twenty days. The results of darkfield examination became negative in from two to eight days (average five days). Stained [3] biopsy material from the lesions showed that spirochetes were present as long as twelve or fourteen days after treatment was started in some instances and long after the results of darkfield examination were negative. The spirochetes, however, were in a fragmented and deteriorated form.

*Secondary Syphilis.*—Of the twenty-seven patients, five were not treated to complete involution for several reasons. One responded well but on the sixth day had severe ptyalism and treatment with sobisminol mass was discontinued. With the other four there was an average of 80 per cent (90, 90, 70, 60) involution in fourteen days. In twenty-two there was complete involution in an average of twelve days. This group was divided as to dose, ten patients receiving six capsules (about 0.84 Gm. of bismuth) daily and twelve receiving nine capsules (1.25 Gm. of bismuth) daily. The first group averaged 12.6 days and the second group 11.6 days for complete involution.

The slight increase in effectiveness achieved with the higher dose seemed to be counterbalanced by a definite increase in gastrointestinal reactions and did not seem to warrant using the higher dose as a routine. In almost all the other groups we found the same situation to hold true, i. e. that the higher dose gave only slightly better results and did not justify the increased incidence of reactions.

*Late Benign Syphilis of the Bones, Skin and Mucous Membrane.*—Of nine patients with cutaneous syphilis, eight had the nodulo-ulcerative and one the palmar squamous form; of the two with syphilis of the mucous membranes, one had gumma of the palate (congenital, tardive) and one gumma of the upper lip and nasal septum. The one patient with syphilis of the bones had acute periostitis (congenital tardive).

In six of the eight patients with nodulo-ulcerative cutaneous lesions, the lesions were completely involuted in an average of thirty-one days (range from twenty-two to forty-three). Of the two whose lesions were not healed completely, the lesions of one had healed 60 per cent at the end of fourteen days, at which time treatment was inadvertently discontinued. The other patient at the time of writing had been receiving treatment forty-two days and his lesions were about 80 per cent involuted.

The squamous palmar lesion healed completely in thirty-three days.

The gumma of the palate was a large gumma of the soft palate in a 12 year old girl with congenital syphilis. This lesion healed completely in twenty days. The gumma of the upper lip and nasal septum was in a middle aged man whose syphilis was treatment resistant and relapsing. The lesion did not show any response whatever to bismuth given orally or to arsenicals but finally responded to fever therapy.

The bone lesion was acute periostitis in a child with congenital syphilis. The sobisminol mass was administered in the milk. Complete involution was achieved in forty-two days.

*Syphilis of the Central Nervous System.*—Sobisminol mass was given to twenty-three patients with neurosyphilis to determine whether this type of bismuth could bring about the relief of symptoms (headache, shooting pains), which we have found consistently with intramuscular administration.

The results obviously depend on the subjective reaction of the patient and therefore are not amenable to exact measurement. However, an effort was made to allow a free expression on the part of the patient, and we did not suggest possible benefits or mention specific symptoms but allowed the patient to volunteer any information he desired.

Of the twenty-three patients, five had such minor complaints that a definite effect could not be determined although in general the results were good. Of the other eighteen almost all had tabetic or meningovascular forms of long duration, all were well familiar with their complaints and all had symptoms severe enough to enable them to appreciate quantitative changes. Of these eighteen, two felt no effect, fifteen felt better and one felt worse. With four the improvement was temporary, lasting less than two months, and with eleven it was prolonged, having lasted more than two months.

Of those who did get benefit, ten stated that they were almost completely relieved of all symptoms. Most of them gained weight as a result of relief from gastric disturbance and subsequent improved appetite. Five stated that they received "fair" improvement.[4]

## TOXICITY AND REACTIONS

Of the ninety patients, seven complained of a bismuth line, ten of stomatitis (three of stomatitis severe enough to warrant interruption of medication), ten of "grip syndrome," thirty of nausea and vomiting, eleven of anorexia, six of diarrhea, one of dermatitis (question-

3. Chambers, S. O., and Scholtz, J. R.: Clinical Application of a Stain for Spirochetes (Krajian), Arch. Dermat. & Syph. **38**: 217 (Aug.) 1938.

4. Subsequent experience has definitely confirmed the impression that sobisminol mass taken orally is unusually effective in giving symptomatic relief to patients with late neurosyphilis, particularly of the tabetic type. This effect has been very striking, immediate and lasting even with patients who had previously received large amounts of bismuth intramuscularly without relief. We consider this situation one of the particular indications for oral (sobisminol mass) therapy.

able), none of headache, four of urinary frequency, two of ptyalism and parotitis and two of esophageal spasm.

Most of the complications were mild so that of the entire group only four had to discontinue treatment permanently and seven temporarily (for from one to three weeks).

One patient had a peptic ulcer. He has taken six capsules daily for seven months with no difficulty.

Two patients had severe esophageal spasm on one occasion. The pain lasted for several days and was so severe that milk and liquids were almost intolerable. One of these patients had hematemesis for two days, although the amount of blood was very small. The obvious explanation seems to be that the capsules had been held in the lower end of the esophagus long enough to dissolve and cause erosion of the mucous membrane.

Of the entire group of ninety patients forty-seven, or approximately 50 per cent, had one or more reactions. It should be noted, however, that most of these were very mild gastrointestinal symptoms (nausea) which lasted only a few hours or days at the most and did not interfere in any way with the treatment. Their importance can be compared to that of the pain and discomfort of varying degrees which most patients complain of at the time of receiving intramuscular injections but which do not last or interfere with treatment.

### RENAL TOLERANCE

Urinary examinations were done for eighty-seven patients (320 specimens).

Four of the patients showed faint traces of albumin in one specimen each. One of these, a 65 year old woman, had been receiving the drug for eighteen months continuously. During this period one specimen showed a 2 plus reaction for albumin, with no other abnormalities. Subsequent examinations over a period of six months gave no further positive results.

One patient showed persistent traces of albumin for several months and granular casts on one occasion. This patient, however, had shown traces of albumin for several months before beginning oral bismuth therapy.

The other two patients each showed a 1 plus reaction for albumin on one occasion. No other abnormalities in the urine were noted. Subsequent urinary examinations on continuation of treatment gave normal results.

All the patients in this group took adequate doses of the drug during the entire period of observation.

### PROLONGED THERAPY

Thirty-eight patients received the drug for two months or more without interruption. Of these, nine were unable to tolerate more than four capsules (0.56 Gm. of bismuth) daily. More than four capsules caused troublesome gastrointestinal reactions.

Five patients have been taking the drug daily for more than a year with no complaints: seven for two months, twelve for three months, four for four months, five for five months, two for six months, one for seven months, two for eight months, two for twelve months, two for fourteen months and one for eighteen months.

The incidence of reactions in this group was similar to that in the general group, i. e. most reactions occurred in the first few days or weeks and thereafter became less frequent, so that most patients had no difficulties whatever after the first two months.

The important feature therefore is that there seems to be no tendency to cumulative toxic effects. Further observation may prove otherwise.

### EVIDENCE OF SUSTAINED THERAPEUTIC EFFECT

In general it can be stated that, so long as daily treatment is continued, the therapeutic effect seems to be sustained. None of our patients had relapse or progression while under treatment except the patient with gumma of the lip, who was treatment resistant from the outset.

On the other hand, from the clinical standpoint we have found certain evidence which suggests that the effect in many instances disappears rather rapidly after treatment is discontinued. In two cases of secondary syphilis, oral treatment with bismuth was carried to complete involution of the lesion (about two weeks), at which time the patients were to be given arsenical therapy. Because of nonattendance of the patients, arsenical therapy was not immediately begun and both showed reactivation of the lesions within two or three weeks.

It has also been observed that in several of our cases of symptomatic neurosyphilis the relief from symptoms is lost within a few weeks after therapy is discontinued, suggesting that a certain level of bismuth in the blood must be maintained for good results and that this level drops rapidly soon after discontinuance of oral medication.

These observations, although far from conclusive, raise an important question which should be investigated. Studies of urinary excretion in human beings will supply a partial answer, and we hope to report soon on such studies.

Sollmann and Cole [5] in recent studies have reported that, "when the administration was stopped, the urinary excretion dropped promptly." Our yet unpublished excretion studies indicate the same conclusion.

### COMMENT ON CLINICAL RESULTS

The results reported allow the following statements:

1. Sobisminol mass administered (daily) in doses containing about 0.84 Gm. of bismuth is absorbed from the gastrointestinal tract in a therapeutically active form in sufficient quantities to bring about involution of active syphilitic lesions of the skin. Involution is achieved in periods comparing favorably with those when preparations for intramuscular administration are used. The time required in cases of primary and secondary syphilis is only slightly greater than when neoarsphenamine is used.

2. Sobisminol mass (orally) in daily doses containing about 0.84 Gm. of bismuth brings relief from the symptoms of late neurosyphilis (particularly tabetic) in a high percentage of cases and appears to offer a definite advantage over any drug heretofore used.

3. Sobisminol mass (orally) is well tolerated by most patients. There is a high incidence of mild gastrointestinal reactions which rarely interfere with treatment. There are no reactions which compare in gravity to the embolism (arterial and venous) and abscess which occur with intramuscular injection with sufficient frequency to make them considerations for concern.

4. Sobisminol mass can be administered every day for many months without producing cumulative toxic effects.

5. Our material does not allow us to say that sobisminol mass (orally) can be substituted for other forms

5. Sollmann, Torald; Cole, Harold, and Henderson, Katharine: Clinical Excretion of Bismuth: V. Excretion of Sobisminol and of Some Other Bismuth Preparations for Oral Administration, Arch. Dermat. & Syph. **37**: 993 (June) 1938.

of bismuth in the routine treatment of early syphilis. All circumstantial evidence points to the fact that sobisminol mass (orally) will do whatever any other bismuth preparation will do, but the ultimate proof lies in a treated series observed for several years.

6. Oral therapy has the disadvantage that its efficiency depends on the intelligence and honesty of the patient (patients are frequently lax and dishonest to their own disadvantage).

7. If oral bismuth therapy receives approval, great care must be exercised in the control of its distribution. Self medication of syphilis is worse than no medication.

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# CONTROL OF PROTHROMBIN DEFICIENCY IN OBSTRUCTIVE JAUNDICE

## BY USE OF VITAMIN K

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Abundant experimental and clinical evidence obtained in the past four years shows that a fat-soluble substance, called by Dam vitamin K,[1] conditions the formation of prothrombin by the liver.[2] In obstructive jaundice at least two factors tending to depress plasma prothrombin are at work, one being damage to the liver and disturbance in its synthetic function and the other the diminished absorption of vitamin K from the intestinal tract. Bile salts have been shown to be necessary for the absorption of fat-soluble substances from the intestinal canal,[3] and in obstructive jaundice the bile delivered into the duodenum may be deficient in bile salts as well as in total volume. Another factor of importance in lowering plasma prothrombin in patients with obstructive jaundice is loss of appetite with inadequate intake of foods containing vitamin K.

The data presented in this report were obtained in the management of cases of obstructive jaundice at the Massachusetts General Hospital during the past twelve months.

### METHODS

Plasma prothrombin was determined by the method of Warner, Brinkhous and Smith, with modifications as previously described.[4] The values are expressed in percentage of normal. Fibrinogen was determined in duplicate on the oxalated plasma by the method of Cullen and Van Slyke, the clot obtained from 1 cc. of plasma being subjected to microdigestion and nesslerization. Plasma bilirubin was measured as follows: Two cc. of plasma was combined with 1 cc. of diazo reagent and allowed to stand ten minutes. Then 2 cc. of saturated ammonium sulfate and 10 cc. of 95 per cent alcohol were added. The mixture was centrifuged, and the color of the supernatant fluid was read against the cobaltous sulfate standard prepared according to McNee and Keefer.[5] Ascorbic acid was determined in the samples of fasting plasma according to Pijoan and Klemperer.[6] The bromsulphalein test was made in the usual way, a calibrated syringe being used to inject a measured quantity of the dye per pound and the concentration in the serum thirty minutes later being read colorimetrically against stock standards. The hippuric acid test was performed as described by Quick.[7] A urea clearance determination was made during the same four hour period, urea in blood and urine being measured by the gasometric method of Van Slyke.[8]

Determinations of plasma prothrombin, bilirubin and fibrinogen were made repeatedly before and after operation.

The vitamin K extract used in this work was prepared from fresh spinach according to the method of Dam, as previously described.[4] Each gram of the vitamin K-cholic acid mixture contained 0.45 Gm. of sodium glycocholate (Merck), 0.45 Gm. of sodium taurocholate (Merck), and 0.1 Gm. of extract derived from 200 Gm. of fresh spinach. In several instances a commercial preparation of vitamin K was used, as noted in the tables.

### RESULTS

In chart 1 are shown data obtained in a case of carcinoma of the head of the pancreas before and after cholecystogastrostomy. The typical preoperative response of prothrombin to vitamin K-cholic acid

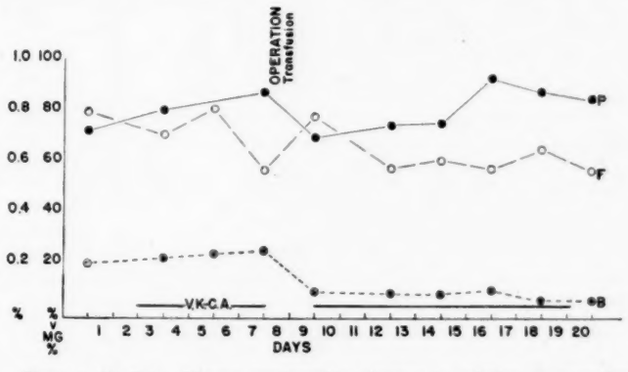


Chart 1 (J. B.).—Plasma prothrombin changes in relation to operation and administration of vitamin K-cholic acid mixture in obstructive jaundice. The mixture, 1.2 Gm. a day, was given orally as shown. *P* indicates plasma prothrombin concentration in percentage, *F* indicates fibrinogen concentration in grams per hundred cubic centimeters, and *B* indicates plasma bilirubin in milligrams per hundred cubic centimeters. This was a case of carcinoma of the pancreas with cholecystogastrostomy.

therapy, the postoperative drop and the secondary response are well shown. There was no abnormal bleeding in this case, as the prothrombin level was kept well above the hemorrhagic zone. Fibrinogen and prothrombin values appear to be unrelated.

The data shown in chart 2 were obtained in the study of a 73 year old patient with carcinoma of the papilla of Vater. The prothrombin value was initially at the dangerously low level of 23 per cent but responded

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1. Dam, Henrik: The Antihemorrhagic Vitamin of the Chick: Occurrence and Chemical Nature, Nature **135:** 652 (April 27) 1935.

2. Dam, Henrik; Schønheyder, Fritz, and Tage-Hansen, Erik: Studies on the Mode of Action of Vitamin K, Biochem. J. **30:** 1075 (June) 1936. Snell, A. M.; Butt, H. R., and Osterberg, A. E.: Treatment of the Hemorrhagic Tendency in Jaundice with Special Reference to Vitamin K, Am. J. Digest. Dis. **5:** 590 (Nov.) 1938. Quick, A. J.; Stanley-Brown, Margaret, and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190:** 501 (Oct.) 1935. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula: Effect of Feeding Bile and Alfalfa (Vitamin K), ibid. **196:** 50 (July) 1938. Stewart.[4]

3. Greaves, J. D., and Schmidt, C. L. A.: The Rôle Played by Bile in the Absorption of Vitamin D in the Rat, J. Biol. Chem. **102:** 101 (Sept.) 1933.

4. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, Ann. Surg. **109:** 588 (April) 1939.

5. McNee, J. W., and Keefer, C. S.: The Clinical Value of the van den Bergh Reaction for Bilirubin in Blood with Notes on Improvements in Its Technic, Brit. M. J. **2:** 52 (July 11) 1925.

6. Pijoan, Michel, and Klemperer, F. W.: Determination of Blood Ascorbic Acid, J. Clin. Investigation **16:** 443 (May) 1937.

7. Quick, A. J.: The Synthesis of Hippuric Acid: A New Test of Liver Function, Am. J. M. Sc. **185:** 630 (May) 1933.

8. Van Slyke, D. D.: Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease, J. Biol. Chem. **73:** 695 (June) 1927.

rapidly to the administration of vitamin K-cholic acid mixture by mouth. Operation was performed with procaine hydrochloride anesthesia and consisted of cholecystoduodenostomy and jejunostomy. The chart shows the temporary postoperative depression in prothrombin and the rapid response to vitamin K-cholic acid given by jejunostomy. There was no abnormal bleeding, and the patient made an uneventful convalescence.

In chart 3 are seen the effects of a bout of cholangitis on prothrombin response to vitamin K-cholic acid therapy. When first studied, the patient's jaundice was of only three days' duration and the prothrombin was only slightly reduced. The subsequent retardation of response to vitamin K therapy illustrates the importance of the condition of the liver, for even though adequate amounts of vitamin K-cholic acid mixture were being taken an improvement in plasma prothrombin concentration did not occur until the fever and jaundice subsided. The plasma fibrinogen values are interesting; they seem to vary inversely with the prothrombin concentrations. Thus with infection plasma fibrinogen rose sharply, while the prothrombin concentration fell even under vitamin K-cholic acid therapy.

In table 1 are shown prothrombin data at the time of massive pathologic bleeding in obstructive jaundice. The danger zone is seen to be below 40 per cent. The patients had either had no vitamin K-cholic acid mixture or else had had insufficient quantities. Proper vitamin K-cholic acid therapy resulted in rapid cessation of bleeding and elevation of prothrombin in all except three cases. The condition of R. G. and M. L. K. was hopeless, and specific therapy and study were

TABLE 1.—*Prothrombin Values at the Time of Massive Pathologic Bleeding Due to Prothrombin Deficiency in Obstructive Jaundice* *

| | | Bleeding | | | | |
|---|---|---|---|---|---|---|
| | Operation | Post-operative Day | Plasma Prothrombin, % | Cell Volume, % | Site | Comment |
| T. P. H. | Cholecystostomy, jejunostomy | 4th | 28.0 | 28.5 | Urinary and biliary tracts | Severe diarrhea, ? absorption vitamin K |
| J. R. B. | Cholecystogastrostomy | 7th | 13.0 | 23.1 | Stomach, gallbladder | Further vitamin K refused 10 days before |
| M. Y. | Repair of common duct | 6th | 31.5 | 34.8 | Wound, gastrointestinal tract | No vitamin K |
| M. L. K. | Exploratory laparotomy | 8th | 25.0 | 46.9 | Wound, uterus | No vitamin K after operation |
| H. C. K. | Choledochostomy | 16th | 36.5 | 30.5 | Wound, gastrointestinal tract | Further vitamin K refused 7 days before |
| R. G. | None; hepatic lymphoblastoma | .... | 24.1 | 37.5 | Mouth, gastrointestinal tract | No vitamin K |
| P. B. | Exploratory laparotomy | 7th | 9.8 | 39.5 | Wound, gastrointestinal tract | No vitamin K |

* Patients had received either no vitamin K-cholic acid mixture or insufficient amounts.

TABLE 2.—*Preoperative Data in Cases of Obstructive Jaundice Due to Stone in the Common Duct* *

| | Age | Sex | Duration of Jaundice, Wk. | Bromsulfalein Retention, % | Hippuric Acid Excretion, Gm. | Urea Clearance, %/Av. Norm. | Fibrinogen, Gm./100 Cc. | Plasma Bilirubin, Mg./100 Cc. | Plasma Ascorbic Acid, Mg./100 Cc. | Prothrombin, Initial, % | Prothrombin After Treatment, % | Duration of Treatment, Days | Dose of Vitamin K-Cholic Acid, Gm. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| L. H. S. | 33 | ♂ | 8 | 100 | 5.4 | 102 | 0.48 | 10.1 | 0.54 | 49.8 | 86.8 | 4 | 3.2 |
| E. J. | 59 | ♂ | 2 | 100 | 2.6 | 135 | 0.29 | 40.0 | 0.30 | 59.2 | 102.0 | 4 | 7.8 |
| M. A. C. | 41 | ♀ | 4 | 70 | 2.0 | ... | .... | 9.9 | .... | 42.4 | 96.4 | 5 | 7.4 |
| D. F. W. | 39 | ♂ | 2 | 25 | 3.1 | 98 | .... | 15.0 | .... | 35.7 | 83.3 | 2 | 5.8 |
| M. L. K. | 61 | ♀ | 8 | 100 | 2.1 | 98 | .... | 13.1 | .... | 70.7 | 100.0 | 5 | 6.0 |
| J. F. | 46 | ♀ | 1 | 70 | 4.7 | 93 | 1.03 | 6.0 | 0.64 | 75.6 | 87.2 | 4 | 3.2 |
| E. L. D. | 70 | ♀ | 2 | 100 | 3.1 | 48 | 0.68 | 12.4 | 0.60 | 77.8 | 101.1 | 6 | † |
| R. D. | 35 | ♂ | 1 | 55 | 3.2 | 68 | 0.32 | 5.5 | 0.36 | 47.1 | 90.3 | 2 | 1.8 |
| J. M. S. | 63 | ♂ | 1.5 | 90 | 3.3 | 75 | 0.57 | 15.5 | 0.92 | 72.9 | 92.6 | 5 | 6.0 |
| G. K. | 71 | ♀ | 4 | 50 | 1.4 | 57 | 0.66 | 5.8 | 0.05 | 81.3 | 108.8 | 3 | 3.6 |
| J. M. S. | 34 | ♀ | 0.5 | 90 | 3.8 | 120 | 0.53 | 9.8 | 1.04 | 95.0 | 110.0 | 6 | 3.6 |
| L. M. N. | 54 | ♀ | 0.5 | 20 | 5.2 | 115 | 0.57 | 2.4 | 0.29 | 76.3 | 93.7 | 5 | 6.4 |
| R. M. | 69 | ♀ | 8 | 45 | 2.7 | 83 | 0.53 | 6.8 | 0.71 | 53.4 | 105.1 | 4 | ‡ |
| E. T. O. | 78 | ♀ | 3 | 100 | 0.6 | 57 | 0.81 | 15.7 | 0.97 | 80.2 | 72.0 | 3 | 3.6 |
| D. P. | 22 | ♀ | 1.5 | 50 | 6.7 | 110 | 0.43 | 9.3 | 0.39 | 68.6 | 100.0 | 3 | 3.6 |
| Average | 51.7 | | 3.1 | 71 | 3.3 | 83.7 | 0.57 | 11.8 | 0.57 | 65.7 | 95.1 | 4.1 | 4.8 |

* Average improvement in prothrombin under treatment, 29.4 per cent.
† Received daily 6,000 units of Vitamin K (Almquist-Stokstad) and 30 grains (2 Gm.) bile salts.
‡ Received daily 3,000 units of vitamin K and 30 grains of bile salts.

TABLE 3.—*Preoperative Data in Cases of Obstructive Jaundice Due to Carcinoma* *

| | Age | Sex | Duration of Jaundice, Wk. | Bromsulfalein Retention, % | Hippuric Acid Excretion, Gm. | Urea Clearance, %/Av. Norm. | Fibrinogen, Gm./100 Cc. | Plasma Bilirubin, Mg./100 Cc. | Plasma Ascorbic Acid, Mg./100 Cc. | Prothrombin, Initial, % | Prothrombin After Treatment, % | Duration of Treatment, Days | Dose of Vitamin K-Cholic Acid, Gm. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| J. B. | 47 | ♂ | 3 | 55 | 3.4 | 57 | 0.79 | 19.2 | 0.32 | 71.4 | 86.6 | 5 | 4.0 |
| H. C. K. | 32 | ♀ | 4 | 90 | 2.7 | 68 | 0.51 | 11.6 | 0.23 | 71.1 | 95.7 | 4 | 3.2 |
| P. W. | 58 | ♂ | 5 | 80 | 5.1 | 63 | 0.50 | 19.6 | .... | 28.9 | 96.1 | 3 | 9.0 |
| J. R. B. | 53 | ♂ | 4 | 70 | 4.4 | 70 | .... | 12.5 | .... | 83.2 | 100.0 | 6 | 24.8 |
| T. P. H. | 66 | ♂ | 6 | 100 | 0.2 | 48 | .... | 43.5 | .... | 28.0 | 56.7 | 2 | 5.7 |
| R. M. | 75 | ♂ | 7 | 65 | 1.2 | 62 | 0.73 | 16.3 | 0.22 | 40.5 | 61.1 | 1 | 0.8 |
| E. W. | 73 | ♀ | 8 | 90 | 1.2 | 78 | 0.67 | 14.2 | 0.61 | 23.1 | 91.9 | 9 | 10.8 |
| D. N. I. | 42 | ♂ | 12 | 85 | 3.8 | 80 | 0.77 | 8.7 | 1.20 | 69.9 | 79.2 | 4 | 5.2 |
| W. T. M. | 54 | ♂ | 4 | 100 | 5.8 | 80 | 0.82 | 21.4 | 0.43 | 67.6 | 81.4 | 9 | 11.2 |
| Average | 55.5 | | 5.8 | 82 | 3.1 | 65.1 | 0.68 | 18.5 | 0.50 | 53.7 | 83.2 | 4.8 | 8.3 |

* Average improvement in prothrombin under treatment, 29.5 per cent.

unjustifiable. Patient T. P. H. had severe liver failure with ascites, anuria, peripheral edema and delirium, and liver function was probably too greatly reduced to make a prothrombin response. Nevertheless, in the last-mentioned case the question is complicated by possible failure of the patient to absorb the mixture fed by jejunostomy on account of brisk diarrhea.

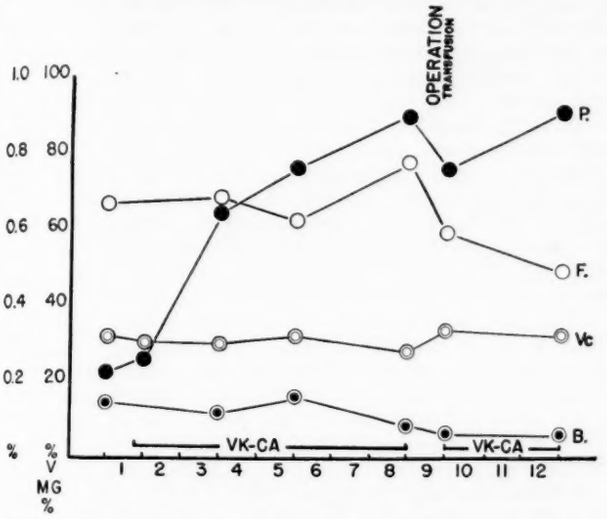


Chart 2 (E. W.).—Plasma prothrombin changes in response to administration of vitamin K-cholic acid mixture, 1.2 Gm. a day, given orally before operation and by jejunostomy after operation. This was a case of carcinoma of the papilla of Vater and cholecystoduodenostomy. *P* indicates plasma prothrombin concentration in percentage, *F* indicates fibrinogen in grams, *Vc* indicates cell volume in percentage and *B* indicates plasma bilirubin in milligrams per hundred cubic centimeters. No pathologic bleeding occurred.

In tables 2 and 3 are shown preoperative data in fifteen cases of obstructive jaundice due to stone and in nine cases due to carcinoma. The data obtained in the liver function tests are of interest in connection with the initial prothrombin response to treatment. Hard and fast conclusions are not to be drawn in such a study, but in general as compared with the patients having obstruction due to stone the patients with carcinoma were jaundiced longer, showed poorer liver and renal function, were more deeply jaundiced and had lower plasma ascorbic acid values and higher fibrinogen values. The plasma prothrombin concentration before and after treatment was definitely lower in the patients with carcinoma. In none of these cases was there failure to establish a safe prothrombin concentration as the result of preoperative treatment. In both groups the plasma ascorbic acid concentration was subnormal, which is indicative of the malnutrition so common in obstructive jaundice.

## COMMENT

The uniformity with which prothrombin deficiency is found in obstructive jaundice is striking. In general terms the longer the duration of the jaundice and the greater the liver damage, the lower the plasma prothrombin concentration. Nevertheless, even as early as three or four days after the onset of biliary obstruction there may be moderate reduction in the prothrombin level, so labile is this factor. There is, on the whole, agreement between clinical appraisement of the patient's condition, the results of liver function tests and the extent of prothrombin deficiency. Further study may indicate that the prothrombin depression is a better index of liver damage than other standard liver function tests.

A question of much interest is the possibility of increasing the prothrombin value to an abnormally high level by heavy vitamin K-cholic acid feeding, with resultant pathologic increase in clotting tendency. In none of the jaundiced patients thus far studied have abnormally high prothrombin values been observed after treatment. There seems to be a rather definite tendency for the prothrombin value to be stabilized close to normal under treatment. The question has been investigated further in a group of patients not suffering from liver disease and having normal prothrombin values. In three such patients from 1.2 to 2.4 Gm. of vitamin K-cholic acid mixture was fed daily for from six to twelve days with no significant change in prothrombin concentration. Since this is two or three times the quantity necessary to restore the level to normal in obstructive jaundice, there evidently exists a considerable margin of safety in administering the mixture.

Reduction in prothrombin of from 20 to 30 per cent is usually seen immediately after operation, probably dependent on such factors as blood loss, anoxemia, effect of anesthetic agent and cessation of intake of vitamin K. In our cases the postoperative drop occurred within the first four days. Since the prothrombin value is so labile, the importance of giving vitamin K with little delay after operation is apparent. For this reason in several instances we have performed jejunostomy at the time of operation on the biliary tract and have continued giving the vitamin without intermission. Occasionally jejunostomy is justifiable for this purpose in preparing a patient for operation, though nasal tube feeding should be tried first if the patient seems unable to take the mixture.

A question of practical importance is How necessary are frequent determinations of plasma prothrombin

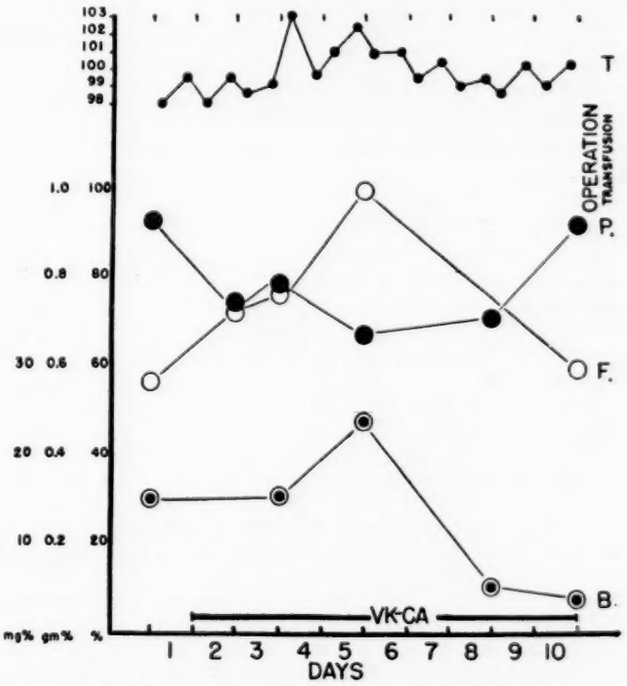


Chart 3 (J. M. S.).—Effect of cholangitis on vitamin K response in obstructive jaundice due to stone in the common duct. Vitamin K-cholic acid mixture, 1.2 Gm. a day, was given orally. *T* indicates oral temperature, *P* indicates prothrombin concentration in percentage, *F* indicates fibrinogen in grams per hundred cubic centimeters, and *B* indicates plasma bilirubin in milligrams per hundred cubic centimeters.

in treating obstructive jaundice with vitamin K-cholic acid mixture? Admittedly the determination is rather tedious and complicated and requires careful attention to details. Eventually knowledge of the subject may be sufficiently satisfactory to warrant routine administration of vitamin K-cholic acid mixture. However,

study of prothrombin concentration is highly desirable until such matters have been settled as the toxicity of vitamin K and cholic acid in obstructive jaundice, the possibility of hyperprothrombinemia, the incidence of refractory hypoprothrombinemia, the purification of vitamin K and the standardization of dosage.

Since the extent of reduction in prothrombin in obstructive jaundice and the ability to respond to vitamin K-cholic acid therapy depend on the degree of depression of liver function, an essential part of the treatment consists of measures known to aid liver function. The patient should receive from 400 to 600 Gm. of carbohydrate daily, by mouth or by vein. Proper amounts of water and sodium chloride must be taken daily, for derangement of liver and renal function makes fluid therapy particularly important. Early decompression of the obstructed biliary tract reduces the damage to the liver cells, and for this reason a two stage operation is often desirable for the sicker patients with neoplastic obstruction to the common duct. In such cases drainage of the gallbladder with local anesthesia after two to four days of preparation may be followed by a safer anastomosis of the gallbladder to the gastrointestinal tract two weeks later.

## CONCLUSIONS

1. Prothrombin deficiency in obstructive jaundice depends on such factors as duration and degree of biliary obstruction, infection, avitaminosis K and malnutrition.
2. Response to administration of vitamin K-cholic acid mixture is immediate except with rapidly progressing liver damage.
3. Massive pathologic bleeding may occur with prothrombin values below 40 per cent.
4. Hyperprothrombinemia during vitamin K-cholic acid therapy was not observed during this study.
5. Important also in treating prothrombin deficiency in obstructive jaundice are administration of dextrose and proper fluids and early decompression of the biliary tract.

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## ABSTRACT OF DISCUSSION

DR. H. P. SMITH, Iowa City: As the authors have stated, patients are definitely in danger of bleeding when the plasma prothrombin level is less than 40 per cent of normal. I think they will agree that vitamin K should be given even when the prothrombin level is as high as 70 per cent. One thereby prevents the patient from falling into the danger zone later on. It is of interest that some patients bleed at the 30 per cent level, whereas others do not. I find that in some cases thrombin develops in clotting blood more rapidly than in others. This is a compensation which to some extent corrects for a deficiency in the amount of prothrombin. It is of interest that in the dog this compensatory mechanism is highly developed, and dogs do not bleed until the prothrombin reaches the astonishingly low level of 10-15 per cent. In man, as the authors pointed out, bleeding commonly begins at the 40 per cent level, but this varies with the degree of compensation present. The fall in the prothrombin level with liver injury is important. This supplements animal experiments which showed a fall in plasma prothrombin when the liver is partially removed or when it is injured by chloroform or phosphorus. It is evident that the liver is a factory concerned in the manufacture of prothrombin. Vitamin K is one of the raw products used by the liver, and without vitamin K the liver cannot perform this important duty. A lowering of the plasma prothrombin level may therefore be due either to shutting off the supply of raw material (vitamin K) or to an injury to the factory—the liver. The feeding of vitamin K corrects the former but not the latter. The suggestion that the prothrombin level be used as a test of liver function is of merit. It must be remembered that the manufacture of prothrombin is merely one of the duties of the liver. It is possible that some types of liver injury depress certain liver functions more than others, and the prothrombin test may not indicate the degree to which certain other functions are depressed. But with this qualification the test should be a valuable addition to the liver function tests already available.

DR. HUGH R. BUTT, Rochester, Minn.: I should like to compliment the authors on their presentation and to ask two questions: First, how long did they allow the concentrates of vitamin K to be mixed with cholic acids before being administered? Second, how long after the administration of vitamin K was the so-called immediate response noticed? The treatment of hemorrhage in patients with jaundice often presents a very difficult problem. For those individuals who have a very low level of prothrombin in the blood it has been the custom to administer rather large doses of concentrates of vitamin K and bile salts through a duodenal tube. In such instances it is perhaps best to mix 1 or 2 Gm. of animal bile salts in 400 or 500 cc. of warm physiologic solution of sodium chloride and add to this 1 or 2 cc. of the crude concentrates. This is mixed well and administered slowly. For some patients it is necessary to repeat this procedure one or more times in order to reduce the clotting time to near normal. The problem of treating patients who are actively bleeding is extremely difficult. Clotted blood often must be removed from the stomach and occasionally the biliary tract must be irrigated before proper absorption of the administered materials can take place. During the past two years my associates and I have encountered a group of patients who had very little jaundice and whose prothrombin levels before and after operation were normal but who nevertheless bled occasionally postoperatively. These patients have been found among the group suffering with acute, subacute and chronic cholecystitis with stones. A few of these patients have had massive hemorrhages, and bleeding in most instances has been controlled by the adequate administration of vitamin K and bile salts. This group of patients emphasizes again the importance of the normal integrity of the liver in the management of hemorrhagic diathesis of patients with jaundice. In other words, jaundice does not necessarily accompany cholemic bleeding in all patients with hepatic injury and, finally, a normal level of prothrombin at the time of operation or after operation does not guarantee against the recurrence of cholemic bleeding at a later date.

DR. L. WALLACE FRANK, Louisville, Ky.: I wish to call attention to the use of vitamin K in the treatment of hemorrhage from the upper gastrointestinal tract. It is not uncommon to see profuse bleeding from this region which is not associated with ulcers and not associated with tumors but is associated with hypertrophic gastritis and duodenitis. In a small series of cases observed since November of last year the blood prothrombin according to the Quick method was estimated at from 65 to 70 per cent of normal when the bleeding began. One of these patients has been observed over a period of five months. He has bled on two occasions and at each time the blood prothrombin was 65 per cent of normal. What initiates bleeding from the upper gastrointestinal tract in this type of case, i. e. hypertrophic duodenitis, is satisfactorily explained by Dr. H. E. Robertson, of the Mayo Clinic. He has demonstrated rather conclusively in such cases that erosion of the mucosa occurs which extends into a more or less rich vascular network in the submucosa. The amount of blood loss varies in relation to the size of the vessels. It is my belief that if the individual's blood prothrombin is high or normal the blood loss will be negligible but if the prothrombin is low the hemorrhage may become alarming. I have used vitamin K in the treatment of such hemorrhage with success.

DR. JOHN D. STEWART, Boston: I am grateful to the discussers for their authoritative comments on this subject. Dr. Butt raised two or three interesting questions. With regard to whether one can say that vitamin K stimulates the formation of prothrombin, this is a difficult question since the exact relationship between vitamin K and prothrombin is not known. It is probably wise to say that vitamin K conditions the formation of prothrombin by the liver in a manner as yet undetermined but with definite quantitative implications. Another question was How long was the mixture of vitamin K and bile salts kept before using in our study? We have used for a period of nine months the same preparation. This has been stored in an ice box at minus 35 C. and has been carefully protected

from sunlight. There has been no recognizable diminution in potency of the mixture during this nine months period, as shown by prothrombin response in patients. Concerning the matter of rapidity of response, the patient's prothrombin concentration was 9.8 per cent at the time of massive bleeding. Twelve hours later, under vitamin K therapy, the prothrombin concentration was 40 per cent. This shows how quickly the remedial effect of vitamin K occurs, provided the substance is absorbed properly from the gastrointestinal tract. An important point is the method of administering the mixture of vitamin K and bile salts. Dr. Butt stated that it may be given through a nasal tube into the duodenum. We have used this technic with satisfaction. Nevertheless there is great need for a pure and effective preparation of vitamin K which can be given parenterally, perhaps eliminating the necessity of the patient's taking bile salts. Progress in this direction is being made. With regard to the reduction in prothrombin in other conditions besides obstructive jaundice of which Dr. Frank spoke, we have encountered such reduction in cases of ulcerative colitis, chronic sepsis and peptic ulcer. We have used vitamin K in treating such cases with apparent success. Dr. Butt tells me that he has recently studied a group of cases with reduction in prothrombin dependent perhaps on a general loss of intestinal mucosal absorptive power, and in such cases there was response to oral administration of vitamin K mixture.

## PRESERVATION OF STORED BLOOD WITH SULFANILAMIDE

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MINNEAPOLIS

Blood transfusion in recent years has become an increasingly important and simplified procedure in most well organized hospitals. The establishment of blood banks and the storing of blood have facilitated the use of this valuable therapeutic agent. The usual technic employed in the United States is that of the Cook County Hospital,[1] consisting of the addition of 0.35 Gm. of chemically pure sodium citrate in physiologic solution of sodium chloride to each hundred cubic centimeters of blood. This gives an adequate amount of sodium citrate for the prevention of coagulation, and after sterility and typing tests and serologic tests for syphilis the blood is available for transfusion for about ten days or more. Standardized serologic tests for typing and for the detection of syphilis give satisfactory results when carefully done. However, sterility tests on stored blood not only are technically hazardous to carry out but also give results difficult to interpret, especially when cultures yield negative results. The importance of determining sterility is usually not seriously considered. None of the reports from different hospitals describe any systematic examination for bacterial contamination after the blood has been stored. Several such articles state that up to 50 per cent of the stored blood is contaminated with bacteria but that its use is not contraindicated. The lack of serious consideration for methods of determining sterility is evidenced in the following statement by Page, Seager and Ward:[2] "Fifty specimens of blood after having been stored for varying periods showed no obvious contamination as evidenced by discoloration of the blood or froth on the surface." The frequency of transfusion reactions, which ranges up to 50 per cent, depending on the index used for defining a transfusion reaction, gives evidence that there may be other factors than those usually considered to be responsible. The utter disregard for bacteria and their by-products in relation to transfusion reactions seems unjustified in the light of knowledge as to the toxic and pyrogenic reactions which they produce within the host. The recent work of Co-Tui and his associates[3] on the production of pyrogens by nonpathogenic bacteria in solutions before intravenous use with resultant adverse reactions in patients receiving such products serves again to emphasize the necessity for exercising the utmost care in the prevention of gross contamination in solutions to be administered intravenously.

As to its source, contamination is most likely to occur when the blood is drawn from the donor. Assuming that all glassware, instruments and solutions used are sterile, there still remain several sources from which the blood can become contaminated. Complete sterilization of the skin previous to phlebotomy is impossible, since there are always a few bacteria which escape the bactericidal action of any cutaneous antiseptic.[4] The needle in its course through the skin may encounter these viable organisms, and the chance for introducing them into the bottle with the blood is high. The addition of the anticoagulant solution to the bottles at the time of drawing the blood from the donor is another possible source of bacterial contamination. Manipulation of the needle in attempts at venipuncture, especially in difficult subjects with small veins, increases the possibility for the inadvertent introduction of a chance contaminant. The likelihood of the presence of a transient asymptomatic or an unrecognized bacteremia in the donor subjects the recipient of such blood to the deleterious action of relatively virulent organisms, since in their new host there is likely to be an absence of the inhibitory substances present in the donor.

TABLE 1.—*Bacterial Population in Blood Containing Sulfanilamide*

| Days | Control | Sulfanilamide Concentration, Mg. per 100 Cc. 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|
| Inoculated with Staphylococcus Albus Isolated from Stored Blood | | | | | | |
| 0 | 380 | 330 | 380 | 290 | 160 | 300 |
| 3 | 404 | 380 | 320 | 310 | 140 | 260 |
| 6 | 12,800 | 390 | 210 | 280 | 108 | 260 |
| 9 | 50,000 | 58 | 100 | 72 | 93 | 62 |
| 15 | 168,000 | 3 | 15 | 13 | 7 | 12 |
| 30 | 172,000 | 0 | 0 | 0 | 0 | 0 |
| Inoculated with Pseudomonas Aeruginosa Isolated from Stored Blood | | | | | | |
| 0 | 26 | 21 | 23 | 19 | 28 | 24 |
| 3 | 240 | 9 | 4 | 5 | 8 | 16 |
| 6 | 19,200 | 7 | 4 | 8 | 7 | 23 |
| 9 | 1,760,000 | 3 | 2 | 2 | 7 | 3 |
| 15 | 2,112,000 | 22 | 7 | 240 | 1 | 49 |
| 30 | 1,900,000 | 86,000 | 38,000 | 124,000 | 64,000 | 72,000 |
| Inoculated with a Hemolytic Spore-Forming Rod Isolated from Stored Blood | | | | | | |
| 0 | 28 | 31 | 23 | 18 | 26 | 30 |
| 3 | 6,400 | 0 | 1 | 1 | 1 | 0 |
| 6 | 72,000 | 0 | 0 | 0 | 0 | 0 |
| 9 | 120,000 | 1 | 1 | 0 | 0 | 0 |
| 15 | 116,000 | 1 | 0 | 0 | 0 | 0 |
| 30 | 164,000 | 0 | 0 | 0 | 0 | 0 |

The reported work on the use of blood from cadavers[5] which is stored for various periods brings up

This work was carried out with the technical assistance of Miss Zora Dragich.
From the Department of Bacteriology and Immunology and University Hospitals, University of Minnesota.

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2. Page, A. P. M.; Seager, K. G., and Ward, E. M.: The Use of Placental Blood for Transfusion, Lancet **1**: 200-202 (Jan. 28) 1939.
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4. Novak, Milan, and Hall, Harry: A Method for Determining the Efficiency of Preoperative Skin Sterilization, Surgery **5**: 560-566 (April) 1939.
5. Shamov, W. N.: The Transfusion of Stored Cadaver Blood, Lancet **2**: 306-309 (Aug. 7) 1937. Yudin, S. S.: Transfusion of Stored Cadaver Blood: Practical Considerations: The First Thousand Cases, ibid. 361-366 (Aug. 14) 1937.

the question of sterility, since the postmortem invasion of the blood stream by bacteria is extremely rapid. In the collection of placental blood [6] the chance for bacterial contamination is far from remote. Hence the possibilities for bacterial contamination are not denied, yet the seriousness of the use of grossly contaminated blood has not been sufficiently emphasized.

The detection of contamination in stored blood is an uncertain procedure, since the number of organisms is usually small. The culturing of 1 cc. of blood from a 500 cc. quantity, as is done as a matter of routine at the time the blood is drawn from the donor, will certainly give questionable results, since a report of sterility may mean merely that the few organisms in the original bottle were not transferred in the portion cultured. The sampling error in the accepted procedure is therefore exceptionally great. On the other hand, the periodic removal of samples for culturing purposes during the period of storage is even more hazardous, since contaminants may be introduced into the flask of blood by this procedure, and hence it cannot be recommended as a routine.

plication of the different strains of organisms involved in contaminated stored blood was sulfanilamide in 1:1,000 concentration. The purpose of the present work is to determine the least amount of the drug needed to produce bacteriostasis for the various periods during which blood is usually stored. The determination of the smallest amount necessary is important, especially when large quantities of the drug are contraindicated or when multiple transfusions are to be given.

## METHOD

The procedure consisted of inoculating 10 cc. of freshly drawn citrated (0.3 per cent) human blood with twenty-four hour cultures of strains of bacteria previously isolated from contaminated stored blood. An attempt was made to introduce less than 3 bacteria per cubic millimeter of blood. Various amounts of sulfanilamide were added to produce final concentrations ranging from 2.5 to 100 mg. per hundred cubic centimeters of blood, except for a control tube which contained no sulfanilamide. After thorough mixing, 0.1 cc. quantities were removed from each sample, added to a tube of molten agar and poured on a Petri plate. This was repeated at regular intervals, during which time the samples remained in a refrigerator at 4 to 6 C. Colonies were counted after a forty-eight hour period of incubation. The results shown in the tables were obtained with the organisms most frequently isolated from contaminated stored blood.

TABLE 2.—*Bacterial Population in Blood Containing Small Amounts of Sulfanilamide*

| Days | Control | Sulfanilamide Concentration, Mg. per 100 Cc. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2.5 | 5 | 7.5 | 10 | 12.5 | 15 | 17.5 | 20 |
| **Inoculated with Staphylococcus Albus** | | | | | | | | | |
| 0 | 300 | 320 | 280 | 320 | 360 | 290 | 400 | 360 | 380 |
| 5 | 187 | 65 | 288 | 25 | 82 | 90 | 86 | 36 | 88 |
| 10 | 206,000 | 116,000 | 960 | 0 | 0 | 3 | 0 | 1 | 2 |
| 15 | 188,000 | 164,000 | 96,000 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 | 230,000 | 184,000 | 136,000 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Inoculated with Pseudomonas Aeruginosa** | | | | | | | | | |
| 0 | 128 | 208 | 390 | 176 | 168 | 142 | 194 | 280 | 180 |
| 5 | 10,240 | 4 | 17 | 4 | 1 | 30 | 1 | 1 | 0 |
| 10 | 4,480,000 | 2,560 | 170 | 1 | 1 | 2 | 0 | 0 | 3 |
| 15 | 3,960,000 | 384,000 | 42,000 | 12,800 | 10,800 | 2,280 | 2,050 | 3,840 | 96 |
| 30 | 3,260,000 | 2,260,000 | 2,420,000 | 1,960,000 | 2,100,000 | 820,000 | 640,000 | 96,000 | 22,000 |
| **Inoculated with Hemolytic Spore-Forming Rod** | | | | | | | | | |
| 0 | 90 | 55 | 54 | 41 | 160 | 120 | 80 | 86 | 27 |
| 5 | 5,120 | 99 | 0 | 0 | 0 | 28 | 30 | 1 | 0 |
| 10 | 120,000 | 320 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 106,000 | 12,600 | 14,200 | 40 | 20 | 20 | 0 | 0 | 0 |
| 30 | 120,000 | 96,000 | 82,000 | 66,300 | 26,000 | 22,600 | 15,200 | 16,800 | 18,600 |

Following the finding of a considerable amount of contamination in stored blood samples, it became obvious that the problem was being neglected. About 5 per cent of blood which had been stored for ten days was found to be grossly contaminated. The organisms found most frequently were aerobic or anaerobic spore-forming rods and staphylococci, both aureus and albus species. Occasionally Pseudomonas aeruginosa was found, and on one occasion a beta hemolytic streptococcus was isolated. Since blood is an excellent menstruum for bacteria, growth of these organisms takes place in blood even at 4 to 6 C., the temperature at which blood is usually stored. Quantitative bacteriologic determinations disclosed the fact that contaminated stored blood contained as many as 2,000,000 organisms per cubic centimeter.

The possibility of using a bacteriostatic substance in doses compatible with intravenous administration was suggested by one of us [7] in a previous paper. Of the several substances investigated, the only one which completely inhibited for as long as six weeks the multi-

These results indicate that for a period of fifteen days a concentration of 20 mg. or less per hundred cubic centimeters is adequate but that for a longer period even 100 mg. is not sufficient in case the contaminant is Pseudomonas aeruginosa. However, since this is a relatively infrequent contaminant and since blood is not often stored for such long periods, the smaller quantities of the drug would usually be sufficient. Table 2 shows results with lesser concentrations of the drug.

The data indicate that a concentration of 20 mg. per hundred cubic centimeters of sulfanilamide is adequate if blood is to be stored up to ten days or two weeks. On transfusion of 500 cc. of blood containing this proportion of sulfanilamide, the amount of the drug introduced would be about 1½ grains (0.1 Gm.), which is an extremely small dose. Since the drug is readily absorbed from the blood by the tissues and since it

6. Goodall, J. R.; Anderson, F. O.; Altimas, G. T., and McPhail, F. L.: Inexhaustible Source of Blood for Transfusion and Its Preservation, Surg., Gynec. & Obst. **66**: 176-178 (Feb.) 1938.

7. Novak, Milan: Use of Bacteriostatic Drugs in Preservation of Blood for Transfusion, Proc. Soc. Exper. Biol. & Med. **41**: 210-211 (May) 1939.

is likewise rapidly excreted, it is doubtful that any detectable elevation of blood sulfanilamide level will result even when multiple transfusions are administered. Since there is progressive deterioration in the various elements of blood, as pointed out recently by Kolmer,[8] and since the control of bacterial multiplication is uncertain, even with sulfanilamide added, in blood stored for longer periods, it does not seem advisable to store blood for more than ten or fifteen days.

The possibility of using sulfanilamide in the preservation of other biologic products is worthy of consideration, since the drug does not tend to precipitate proteins, as frequently happens when other preservatives are used.

SUMMARY

1. Contamination of stored blood with bacteria has not been considered seriously enough in the past.

2. Many unexplained transfusion reactions may be due to pyrogens or other bacterial by-products in contaminated blood.

3. Complete bacteriostasis of the usual bacterial contaminants in stored blood is made possible by the addition of 20 mg. per hundred cubic centimeters of sulfanilamide. Such blood will not only not support bacterial growth for ten to fifteen days but may actually become sterile in that time.

4. Sulfanilamide may prove valuable as a preservative in other biologic substances.

## Clinical Notes, Suggestions and New Instruments

### ACETANILID POISONING

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Acetanilid poisoning presents a clinical picture which is of importance because of the incorporation of the drug in popular, widely advertised headache remedies. Cases of poisoning were reported as far back as 1886 by Eisenhardt[1] and 1890 by Herrmann.[2] The number of such reports varied with the current popularity of preparations containing the drug. In the early years of the present century Stewart,[3] Herrick and Irons[4] and others cited many instances of poisoning.

Two types of poisoning from acetanilid may occur. The acute form may be seen after ingestion of a normal therapeutic dose (0.2 Gm.) if there is an idiosyncrasy, as has been reported by Lundsteen, Meulengracht and Rischel,[5] or after ingestion of the drug in dosage ordinarily regarded as toxic. However, as much as 4 Gm. has been taken at one time with no apparent ill effect. Acute acetanilid poisoning is characterized mainly by cyanosis, chills, exanthems, abdominal distress with vomiting, diffuse neurologic disorders, coma, circulatory collapse and occasionally death from cardiac failure. In cases of chronic poisoning, in addition to any of the manifestations already mentioned, there are commonly anorexia, so-called aniline cachexia, asthenia and secondary anemia. Herrick and Irons[4] called attention to the splenomegaly which occasionally occurs. Cases combining features of both acute and chronic poisoning are frequent.

8. Kolmer, J. A.: Preserved Citrated Blood "Banks" in Relation to Transfusion in the Treatment of Disease with Special Reference to the Immunological Aspects, Am. J. M. Sc. **197:** 442-452 (April) 1939.

From the Mount Sinai Hospital.

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2. Herrmann, E.: Deutsche. med. Ztg. **11:** 865, 875, 1890.
3. Stewart, D. D.: Chronic Poisoning by Acetanilid, J. A. M. A. **44:** 1725 (June 3) 1905.
4. Herrick, J. B., and Irons, E. E.: Chronic Acetanilid Poisoning, J. A. M. A. **46:** 351 (Feb. 3) 1906.
5. Lundsteen, E.; Meulengracht, E., and Rischel, A.: Chronic Acetanilid Poisoning, Acta med. Scandinav. **96:** 462, 1938.

#### REPORT OF CASE

*History.*—C. A., a white man aged 46, a soda fountain attendant, had for many years had severe right frontoparietal headache suggestive of migraine; this had been markedly worse during the two months before admission to the Mount Sinai Hospital. A right intranasal antrotomy four years before admission did not relieve the headache. "Bromo Seltzer," taken on an average of five times a day, was fairly efficacious in relieving the headache prior to the two months of aggravated symptoms, during which time from fifteen to twenty standard soda fountain doses were taken every day with little if any effect (each dose contains approximately 0.24 Gm.). Four days before admission the patient complained of malaise and anorexia. The temperature was 103 F. and there was mental clouding. There were two episodes of vomiting. The temperature dropped to normal during the next three days, but the mental aberration became worse. No medication was taken during this time. On admission the patient was disoriented and stuporous.

*Examination.*—The patient was semicomatose, pale and thin, with a striking dusky, grayish cyanosis, especially of the lips and finger nail beds, which were violaceous. The heart sounds were of fair quality. A few crepitant rales were heard at the left base. The pulse was thready. Abdominal examination was negative and there was no adenopathy. The blood pressure was 108 systolic and 74 diastolic.

Neurologic examination revealed that the pupils were equal and reacted sluggishly to light and in accommodation. There was bilateral nystagmus. There was intention tremor with asthenia and asynergia. The deep reflexes were hyperactive, more on the right than on the left side. The right cremasteric reflex was diminished and there was a bilateral Oppenheim reflex. The Babinski sign was absent.

Laboratory Data: The hemoglobin content was 84 per cent (Sahli). The white blood cell count was 7,800. The differential count showed 77 polymorphonuclear leukocytes, of which 16 were nonsegmented cells, 14 lymphocytes, 8 monocytes and 1 eosinophil. The urine was a dark reddish brown and had a yellowish foam. A trace of bile was found, and urobilin was present in concentration of 1:60. The icteric index was 3 and the blood urea nitrogen was 14 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Lumbar puncture showed clear fluid under pressure of 120 mm. of water, with no block. Reaction to the Pandy test was negative. Microscopic examination showed 3 lymphocytes. The Wassermann test on the spinal fluid and the colloidal gold test gave negative results. Spectroscopic examination of the blood failed to show the absorption band for methemoglobin or sulfhemoglobin. Although the urine remained dark for five days, bile was reported absent from the later specimens. The indophenol reaction for para-aminophenol was equivocal. X-ray examination of the chest showed no abnormality.

*Course.*—There was rapid improvement with administration of abundant fluids. The psyche was completely clear after a week of hospitalization. The abnormal neurologic signs disappeared, although the tremor of the hands persisted. The handwriting, which was a scrawl shortly after admission, became legible. A second white blood cell count was 18,000 with 80 per cent polymorphonuclear leukocytes and 20 per cent lymphocytes; hemoglobin was 90 per cent (Sahli) and the red blood cell count was 5,000,000. The temperature, which was 100.6 F. on admission, became normal on the third day and remained so until discharge ten days later. The headaches were immediately and entirely relieved by withdrawal of the drug. However, they recurred, but only infrequently (about once a month), lasting from twelve to twenty-four hours, after the patient was discharged. They were unaffected by the intramuscular administration of ergotamine tartrate but have been relieved by acetylsalicylic acid (0.6 Gm.).

#### COMMENT

Cyanosis, the most frequent presenting sign in acetanilid poisoning, may be present in varying degrees. It is not due to oxygen unsaturation but to the presence of the dark colored

oxidation products of para-aminophenol,[6] and perhaps to the presence of methemoglobin or sulfhemoglobin.

Tolerance to the drug is built up after continued use. For occasional use, for headache or lassitude, acetanilid is a powerful analgesic preparation of great value. However, if it is abused there is actually a tendency toward production of headache with the resulting establishment of a vicious circle. Presumably this was true in the case described, since withdrawal of the drug resulted in practically complete disappearance of the headache. If the drug is stopped abruptly after a long period of use there may be withdrawal symptoms of variable severity.

The treatment of acetanilid poisoning is not difficult unless symptoms of withdrawal are marked. Ordinarily, forcing of fluids by all available routes is sufficient. If the patient suffers from lack of the drug, withdrawal symptoms can be alleviated by the administration of small doses. Smith[7] found that the addition of sodium bicarbonate to acetanilid in a molecular ratio of 1:2 reduces the mortality of experimental rats, so this drug might be used to therapeutic advantage. Collapse should be treated as is collapse from any other cause. Symptomatic treatment adds to the patient's comfort. Most of the symptoms disappear after elimination of the drug, although neurologic manifestations occasionally persist.

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## SPOOL COTTON AS A SUTURE MATERIAL

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Whereas there has been a noticeable trend toward the use of nonabsorbable suture materials, particularly silk, in the past five years, undoubtedly the average physician fears nonabsorbable sutures because pathologists and some of the older surgeons have emphasized that "foreign bodies" are detrimental to tissues. This fear has deterred him from using nonabsorbable suture materials and has been justified by the poor results obtained from their incorrect use.

As Guerry[1] and Gage[2] have used successfully fine spool cotton as ligatures for many years, it occurred to us that the same material in proper sizes might also be used throughout major operations. Susruta about 500 B. C.[3] recommended

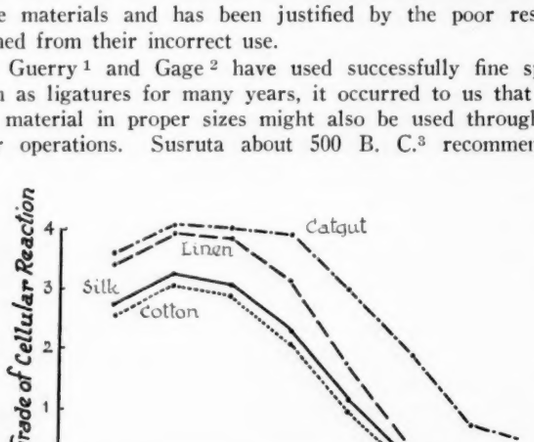


Chart 1.—Grade of cellular reaction of various suture materials.

cotton for the suture of wounds of joints and the abdomen and recently Ginkovskiy,[4] after considerable experimental animal work, advocated the use of cotton in surgical procedures on man.

In a previous paper we[5] showed the comparative reactions of tissue (rabbit) to catgut, silk, linen and cotton sutures (chart 1). The last produced less cellular exudation and earlier healing than any of the others. Whereas dry cotton has less tensile strength size for size than catgut, silk or linen after being placed in tissues, it showed much less decrease in tensile strength (break strength) than the others (chart 2). Halsted[6]

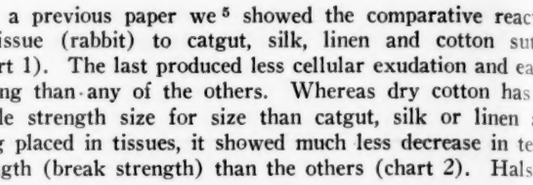


Chart 2.—Alteration in tensile strength of suture materials placed in tissues as compared with the tensile strength of the respective sutures before tissue implantation. The suture material was sterilized and then a portion of it was used for determining tensile strength. This tensile strength was taken as 100 per cent. The remaining sterile portion of the suture material was embedded in tissue for varying periods, from two days up to eighteen, at which time the tensile strength was determined and the percentage decrease in the tensile strength calculated. As shown, there was no change in the tensile strength of cotton until after the tenth day, whereas with the other materials there was a progressive decrease in tensile strength in material which had been placed in tissue.

and Howes and Harvey[7] showed that there was no need for using a suture which had greater tensile strength than the tissue in which it was placed. Unquestionably there is a tendency for many surgeons to strangulate and mutilate tissue when handling sutures of great strength.

Catgut and the materials used in its preparation for use as a suture, chromic acid salts, tannates, iodine, copper and solution of formaldehyde are all deterrents of "dry" wound healing. These chemicals, in addition to the animal protein, produce an inflammatory reaction characterized by an increased exudation which Gage[2] has termed "wet" type of healing, whereas cotton and silk produce little inflammatory reaction, thus resulting in a "dry" type of healing which is associated with early fibroblastic proliferation.

Ordinary and mercerized spool cotton thread is made from long fiber sea-island and Egyptian cotton. The ordinary spool cotton is made up of six twisted cords and the mercerized of three. In contrast to silk, which is a keratin-like protein, cotton is cellulose. Our investigations[5] showed that there was practically no tissue ingrowth in cotton sutures in contrast to silk, in which each fibril is separated from the other by fibrous tissue. The lack of tissue ingrowth can be explained by the compactness of the cotton thread, which is due to the natural twist of fibril. We believe that the ingrowth of granulation tissue into the silk suture is responsible for the development of the occasional silk sinus, and for the same reason cotton will not produce sinuses because infected tissue cannot invade the suture.

A bacteriologic examination of unsterilized cotton thread showed, besides the ordinary pyogenic organisms, an anaerobic one which resembled Bacillus histolyticus in its cultural characteristics. B. welchii and related gas organisms and B. tetani could not be demonstrated in eighty different samples. All contaminants were killed by boiling for twenty minutes or by autoclaving for fifteen minutes at 15 pounds pressure (cultured

6. Young, A. G.: Hematological Studies of Anilin Poisoning, J. Pharmacol. & Exper. Therap. **27:** 125 (March) 1926. Young, A. G., and Wilson, J. A.: Toxicological and Hematological Studies of Acetanilid Poisoning, ibid. **27:** 133 (March) 1926.

7. Smith, P. K.: Effects of Sodium Bicarbonate on the Antipyretic Action and Toxicity of Acetanilid, J. Pharmacol. & Exper. Therap. **58:** 192 (Oct.) 1936.

From the Department of Surgery, Tulane University of Louisiana School of Medicine.

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2. Gage, I. M.: Personal communication to the authors.

3. Melle, G. J.: Early History of the Ligature, South African M. J. **8:** 290 (April 28) 1934.

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7. Howes, E. L., and Harvey, I. C.: Tissue Response to Catgut Absorption, Silk and Wound Healing, Correlation with Tensile Strength, Internat. J. Med. & Surg. **43:** 225 (April) 1930.

aerobically and anaerobically in beef broth bouillon and litmus milk for fifteen days).

When boiled for twenty minutes, cotton thread increases 10 per cent in tensile strength, whereas silk changes but little (chart 2). When placed in tissue it loses 10 per cent of its tensile strength in fourteen days, whereas catgut loses from 50 to 70 per cent and silk 35 per cent. Owing to cotton's greater coefficient of friction, a square knot holds better than it does in silk or catgut, making it possible to cut the suture closer to the knot. However, when mercerized cotton is used to coaptate tissue under tension a triple throw knot should be tied and then the suture cut on the knot.[8]

In the use of cotton as with silk, we follow strictly the tenets of Halsted,[6] which were (1) to use interrupted sutures only, (2) never to use coarse suture material, (3) never to bridge over a dead space as a chord substends an arc, (4) to use transfixion sutures in ligation, as finer material could be used in this way, (5) to use a greater number of fine stitches rather than a few coarse ones and (6) to avoid the combined use of buried absorbable and nonabsorbable sutures. If these rules are disregarded trouble is likely to follow, as we have unfortunately experienced.

Spool cotton thread, plain and mercerized, has been used throughout 196 operations, among which were thyroidectomies, radical and simple mammectomies, herniorrhaphies, intestinal obstructions, perforated peptic ulcers, cholecystectomies, appendectomies, colostomies, thoracoplasties, tenorrhaphies, splanchnic resections, gastro-enterostomy, pneumonectomy and ligation of an external carotid artery. In the group were three serious and two minor postoperative infections. All healed without sinus formation and without extrusion or removal of a suture. One of these cases we are reporting in detail:

A Negro woman aged 50 entered Charity Hospital complaining of a large tumor on her head. Before surgical attack was made on the tumor it was decided to do a ligation of the left carotid. This was done, but considerable difficulty was experienced because of the large veins of the neck. A large lymph node was encountered and punctured with tissue forceps in its removal. The external carotid was ligated with no. 20 crochet cotton, all other vessels being ligated with transfixion ligatures of no. 50 plain cotton and the skin closed with cotton. On the fifth day the wound suppurated and by the eighth day the entire wound was open. Following irrigation with azochloramid, the granulations became clean and adhesive strapping was applied, the wound being closed entirely by the thirty-eighth postoperative day. No sutures were seen to come from or were removed from the wound. The temporal artery on that side remained occluded.

We recommend and have found satisfactory no. 60 plain cotton for the ligation of small vessels of the subcutaneous fat and other areas, no. 30 plain cotton or "heavy duty" mercerized cotton for approximation of the peritoneum and fascia. Where retention sutures are employed, no. 20 crochet cotton may be used. For through and through sutures of the abdominal wall no. 10 mercerized crochet cotton is best. Skin closure, when tension is not a factor, can be readily accomplished with no. 50 black mercerized thread. Black is used instead of white because the latter is somewhat difficult to find at times, owing to its becoming stained with blood. The cotton thread should be sterilized on a spool which does not expand in water as the cotton shrinks, causing the fibers to be broken. From a technical standpoint it is better to put all the sutures in one layer and then tie, as the tension is then transmitted to all the sutures, and besides time is saved. When there is an opportunity for serum to accumulate in the wound we have for some years used marine sponge compression bandages. We do not drain wounds unless there is gross contamination of abdominal wounds, in which a rubber tissue drain is placed down to the transversalis fascia and peritoneum. Because of its availability and the ease with which it can be sterilized, cotton thread would be a very satisfactory suture in field hospital in wartime.

8. Taylor, F. W.: Surgical Knots and Sutures, Surgery **5**: 498 (April) 1939.

SUMMARY

1. Cotton thread has been found to be an extremely satisfactory suture, as it is easily sterilized and flexible and produces little tissue reaction and early fibroplasia.

2. Boiling for twenty minutes or autoclaving for fifteen minutes at 15 pounds pressure with the cotton wound on a rubber spool is recommended.

3. Of 196 operative procedures carried out, healing by primary intention occurred in 191.

4. There were three serious and two minor infections, all of which healed without sinus formation.

5. Halsted's rules concerning the use of silk were strictly adhered to in the use of cotton.

6. There is considerably less decrease in the tensile strength of cotton in tissue than that of catgut, silk or linen.

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## PLASMA PROTHROMBIN CONTENT OF BANK BLOOD

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Recently Rhoads and Panzer [1] have stated that "bank blood" is an unsatisfactory source of plasma prothrombin for the treatment of patients with the hemorrhagic tendency associated with jaundice. Their results were based on the determination of the plasma prothrombin content of bank blood by the method of Quick.[2]

Quick's method for the determination of plasma prothrombin controls two of the four important factors which enter into the formation of a clot. An excess of calcium and thromboplastin are added to oxalated plasma in suitable amounts, and the time taken for a clot to form is considered the prothrombin time. In the Quick test no attempt is made to control the fibrinogen in the plasma. Linton [3] and Moss [4] have demonstrated that the fibrinogen in the plasma of man and dogs is normal in the hemorrhagic tendency associated with obstructive

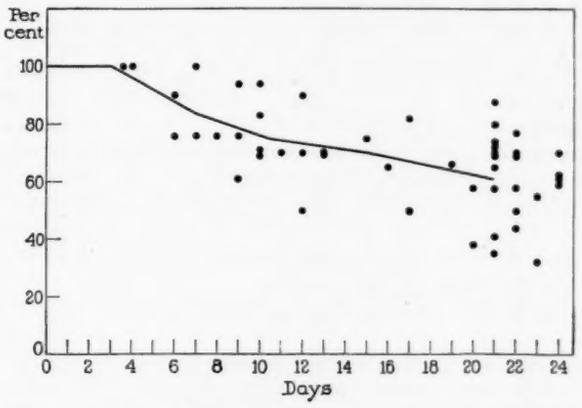


Fig. 1.—Prothrombin content of forty-nine samples of bank blood.

jaundice. On the basis of their data, Quick [5] considered it unimportant to control the factor of fibrinogen in the clotting process.

In 1935 Warner, Brinkhous and Smith [6] described a method for the determination of plasma prothrombin which controlled

This study was carried out under a grant from the John and Mary R. Markle Foundation.

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1. Rhoads, J. E., and Panzer, L. M.: The Prothrombin Time of "Bank Blood," J. A. M. A. **112**: 309-310 (Jan. 28) 1939.

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4. Moss, Walter: Experimental Obstructive Jaundice: Its Effect on Fibrinogen and Coagulation of the Blood, Arch. Surg. **26**: 1-19 (Jan.) 1933.

5. Quick, A. J.: The Nature of the Bleeding in Jaundice, J. A. M. A. **110**: 1658-1662 (May 14) 1938.

6. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations under Experimental Conditions, Am. J. Physiol. **114**: 667-675 (Feb.) 1936.

the factor of fibrinogen as well as the calcium and thromboplastin. Their test is a titration method involving several steps which are, briefly, as follows: Oxalated plasma is rendered fibrinogen free by the addition of freshly prepared thrombin. The prothrombin which is present in the fibrinogen-free plasma is then converted to thrombin by the addition of standard amounts of calcium and thromboplastin. To this thrombin is added standard solution of fibrinogen, and the time for a clot to form is determined. The fibrinogen-free plasma is diluted sufficiently to allow a clot to form in fifteen seconds after the addition of fibrinogen. The limits of error of the titration

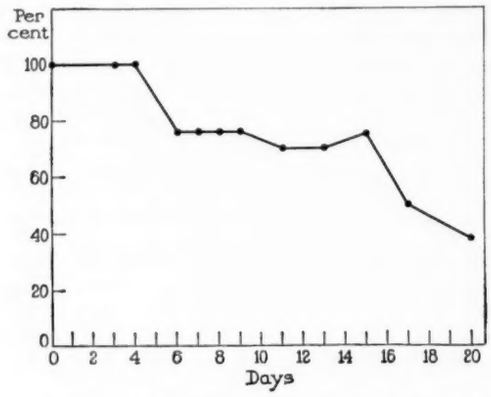


Fig. 2.—Prothrombin content of a single sample of bank blood.

method of determining plasma prothrombin in the hands of Warner, Brinkhous and Smith and of ourselves is about 15 per cent.[7] Either sodium citrate or sodium oxalate may be used as the anticoagulant.

The present study has been divided into two parts: first, the determination of the levels of plasma prothrombin in samples of bank blood after a suitable interval of storage employing the methods of Quick [2] and of Warner, Brinkhous and Smith,[6] and second, observation of the influence on plasma prothrombin of exact refrigeration as employed in the blood bank and to be described by one of us (J. B. P.). The plasma prothrombin of blood from the blood bank is contrasted with the plasma prothrombin of blood stored in the usual laboratory refrigerator. Samples for prothrombin determination were taken directly from the blood as it was being administered to the patient. The blood in the blood bank was maintained at a temperature of 2 to 4 C. The data are shown in the table. As Rhoads and Panzer [1] observed, when the method of Quick is used the plasma prothrombin falls rapidly to less than 30 per cent of normal in less than one week. In contrast, the level of plasma

*Plasma Prothrombin Content of Bank Blood* *

| | Blood Bank | | | Typical Ice Box | |
|---|---|---|---|---|---|
| Days | No. of Samples | Quick Test, % | W., B. & S. Test, % | No. of Samples | W., B. & S. Test, % |
| 1- 5 | 2 | 35 | 100 | 6 | 93 |
| 6- 8 | 5 | 23 | 84 | 6 | 79 |
| 9-12 | 11 | 27 | 75 | 6 | 48 |
| 13-17 | 6 | 22 | 69 | .. | .. |
| 18-24 | 25 | 14 | 61 | .. | .. |

* The figures indicate percentages of normal content.

prothrombin of the same samples of bank blood when tested by the method of Warner, Brinkhous and Smith shows a gradual and gentle fall, remaining above 60 per cent of normal after three weeks of storage.

The explanation of the significant difference between the levels of plasma prothrombin of blood when determined by the method of Warner, Brinkhous and Smith on the one hand and by the method of Quick on the other is not clear. The fibrinogen content of the samples of bank blood was determined by the method of Bancroft and his co-workers,[8] and no significant change in the average level of fibrinogen occurred during the three weeks of storage. It is possible that after storage there are qualitative changes in the fibrinogen so that it does not react with thrombin as quickly or as completely as fresh blood.

In the table, plasma prothrombin of blood from the blood bank is contrasted with plasma prothrombin of blood stored in the typical laboratory electric ice box. There is only a slight difference, i. e. 5 per cent, in the level of plasma prothrombin stored by the two methods during the first week; but by the ninth to twelfth day there is a marked loss of plasma prothrombin in the inadequately refrigerated blood, the level falling to an average of less than 50 per cent in contrast to an average of 75 per cent for the properly stored bank blood.

Figure 1 is a spot graph of the plasma prothrombin levels, as determined by the method of Warner, Brinkhous and Smith, of the forty-nine samples of rigidly stored bank blood. During the first ten days no sample has fallen to as low a level as 60 per cent of normal, and not until the twentieth day does any sample show less than 50 per cent of normal. Figure 2 shows the plasma prothrombin levels of a typical specimen of bank blood followed over a period of twenty days.

### SUMMARY

1. On the basis of the method of Warner, Brinkhous and Smith, bank blood is an adequate source of plasma prothrombin for about nine days. At longer intervals of storage the plasma prothrombin declines gradually, reaching the level of 61 per cent of normal by the end of the third week of storage.

2. Carefully controlled refrigeration of bank blood is an important factor in the preservation of plasma prothrombin.

## THE QUANTITY OF BLOOD REQUIRED TO PRODUCE A TARRY STOOL

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This experiment was undertaken under the direction of Dr. A. C. Ivy to ascertain the quantity of blood which, when taken by mouth, will produce a tarry stool.

Ten healthy medical students were the subjects of the experiment. The procedure employed was essentially the drinking of venous blood drawn from the subject and subsequent gross examination for a tarry stool; that is, a stool which was black and glistening. No microscopic or chemical tests for blood were used, for the results of such an examination are not obtained in a patient's history. Progressively larger quantities of blood were taken by the subject until a tarry stool occurred. Sufficient time in each case was allowed for passage of the blood through the gastrointestinal tract before larger quantities were taken. Each subject was allowed to eat a general diet of his own choice; in addition, four of the students repeated the experiment while on a diet of milk and cream, which was used to obviate any possible blackening of the stool by a general diet.

Of the ten students who took the blood while on a general diet, one had a tarry stool after taking 50 cc., two with 60 cc., three with 70 cc. and four required 75 cc. of venous blood. A tarry stool was obtained with 55, 60, 70 and 80 cc. by the four students on the milk and cream diet. In two cases this amount of blood was the same as that required on a general diet; in the other two 5 and 10 cc. more of blood was required to produce a typical tarry stool on the general than on the milk and cream diet.

### CONCLUSION

At least from 50 to 80 cc. of blood when taken by mouth is required for the production of a tarry stool.

12 West Walton Place.

7. The limits of error of the Warner, Brinkhous and Smith test of about 15 per cent refers to the test as run from day to day. When several samples are run at one time, the limits of error are less than 3 per cent.

8. Bancroft, F. W.; Stanley-Brown, M., and Quick, A. J.: Postoperative Thrombosis and Embolism, Am. J. Surg. **28**: 648-668 (June) 1935.

## *Special Article*

# THE NEW FEDERAL FOOD, DRUG AND COSMETIC ACT

### A CONSIDERATION OF FEATURES THAT ARE OF PARTICULAR INTEREST TO THE MEDICAL PROFESSION

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The Federal Food, Drug and Cosmetic Act was enacted into law on June 25, 1938. On that date the sections pertaining to new drugs, dangerous drugs and injurious cosmetics became effective. Other provisions became operative only to the extent that they may relate to the enforcement of the aforementioned sections. The act was to have become effective in its entirety on June 25, 1939, but meanwhile an amendment was enacted postponing the new labeling requirements until Jan. 1, 1940, or later under certain conditions.

The old Food and Drugs Act was passed in 1906 when social, economic and technologic conditions in this country were vastly different from those which obtain today. During the intervening thirty-two years repeated efforts to adapt food and drug legislation to changing conditions and the growing complexity of our national life were invariably successfully opposed until the act of 1938 was passed. It is generally conceded that this law, while inadequate and defective in certain respects, is a genuine improvement over the original act. From a long range point of view, the extent to which this improvement will be translated into actual accomplishment will depend largely on three factors: (1) the manner in which the provisions of the act are interpreted by the federal courts, (2) the extent to which Congress is willing to implement its enforcement through adequate appropriations and (3) the cooperation of scientific and professional groups and consumer groups.

Certain features of the new act should be of special interest to members of the medical profession. The Food, Drug and Cosmetic Act of 1938:

1. Brings under control drugs used in the diagnosis of disease and drugs intended to affect the structure or any function of the body [sec. 201 (g) (2), (3)]. (Under the old law, only substances intended to be used for the prevention, cure or mitigation of disease were classed as drugs.)

2. Brings therapeutic devices under control and subjects them to the same general requirements as are set up for drugs [sec. 201 (h), secs. 501, 502].

3. Brings all cosmetics except soap under control [sec. 201 (i)], outlaws cosmetics which may be injurious to users, except coal tar hair dyes, which must bear warning labels and carry adequate directions for preliminary testing of the skin [sec. 601 (a)] and prohibits false or misleading labeling on cosmetics [sec. 602 (a)].

4. Prohibits traffic in drugs and devices which are dangerous to health under the conditions of use prescribed in the labeling [sec. 502 (j)]. (The old act contained no prohibition against dangerous drugs or devices.)

5. Prohibits traffic in new drugs unless such drugs have been adequately tested to show that they are safe for use under the conditions of use prescribed in their labeling, and authorizes exemption from this requirement of drugs intended solely for investigational use by qualified scientific experts [sec. 505].

6. Requires drugs intended for use by man to bear labels warning against habit formation if they contain any of a list of narcotic or hypnotic habit-forming substances, or any derivative of any such substance which possesses the same properties [sec. 502 (d)].

7. Requires the labels of nonofficial drugs to list the names of the active ingredients and in addition to show the quantity or proportion of certain specified ingredients. Authorizes regulations prescribing exemptions from this requirement when compliance is impracticable [sec. 502 (e)].

8. Requires the labeling of drugs and devices to bear adequate directions for use but authorizes regulations exempting drugs and devices from this requirement when it is not necessary for the protection of the public health [sec. 502 (f)].

9. Exempts a drug dispensed on the written prescription of a licensed physician and the label of which contains the name and place of business of the dispenser, the serial number and date of such prescription and the name of such physician from the labeling requirements relating to:

(*a*) Name and address of manufacturer and statement of quantity of contents [sec. 502 (b)].

(*b*) Declaration of the name of the drug or the common names of the active ingredients when the drug is fabricated from two or more ingredients, and declaration of the quantity of certain specified ingredients [sec. 502 (e)].

(*c*) Declaration of "Warning—may be habit forming," when the drug contains the substances mentioned in section 502 (d) or their derivatives but only in those cases in which the prescription is marked as not refillable or its refilling is prohibited by other laws [sec. 502 (d)].

10. Requires the labeling of drugs and devices to bear warnings against use in those pathologic conditions or by children when its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form as are necessary for the protection of users [sec. 502 (f)].

11. Requires special precautionary packaging and labeling as the Secretary of Agriculture may determine to be necessary for drugs that are liable to deterioration [sec. 502 (h)].

12. Requires labels of official drugs—i. e. drugs recognized in the United States Pharmacopeia, National Formulary or Homeopathic Pharmacopeia of the United States—to reveal any differences of strength, quality or purity from the official standards [sec. 501 (b)]. (The old law requires merely that the label bear a true statement of the strength, quality and purity of the drug without showing the difference from the official standard.)

13. Makes the Homeopathic Pharmacopeia of the United States the legal standard for homeopathic drugs [sec. 201 (j), sec. 501 (b)].

14. Requires official drugs to be packaged and labeled as prescribed by the pharmacopeias and National Formulary [sec. 502 (g)].

15. Declares nonofficial drugs illegal if the standard of strength thereof differs from, or the purity or quality falls below, the standard claimed [sec. 501 (c)]. (The old law prohibits only those which fall below the strength claimed.)

16. Requires that antiseptics possess germicidal power [sec. 201 (o)].

17. Does not contain the fraud joker in the old law under which the government must prove that false claims of curative effect on the labels of "patent medicines" were made with wilful intent to deceive.

18. Proscribes the use of containers for food, drugs and cosmetics which may render the contents injurious to health [sec. 402 (a) (6), sec. 501 (a) (3), sec. 601 (d)].

19. Prohibits traffic in food, drugs and cosmetics which have been prepared or handled under insanitary conditions that may contaminate them with filth or cause them to contain any putrid or decomposed substance or that may render them injurious to health [sec. 402 (a) (4), sec. 501 (a) (2), sec. 601 (c)].

20. Forbids the use of uncertified coal tar colors in foods; also in drugs when used for coloring purposes only, and in cosmetics other than hair dyes [sec. 402 (c), sec. 501 (a) (4), sec. 601 (e)].

21. Proscribes slack filling of containers for food, drugs and cosmetics and prohibits the use of deceptive containers [sec. 403 (d), sec. 502 (i) (1), sec. 602 (d)].

22. Prohibits traffic in food which may be injurious to health [sec. 402 (a) (1)]. (The old law prohibited injurious food only when the poisonous substance was added.)

23. Prohibits the addition of poison to food except when such addition is required in the production thereof or cannot be avoided by good manufacturing practice; when added poisons are so required or cannot be avoided, tolerances are authorized, the amount being limited to a point insuring protection of public health [sec. 402 (a) (2), sec. 406 (a)].

24. Authorizes emergency permit control of food that may be injurious because of contamination with microorganisms if public health cannot otherwise be protected [sec. 404]. Through the operation of this provision the continued distribution of such food, or food suspected of contamination, can be stopped until the situation is fully corrected.

25. Forbids traffic in confectionery containing metallic trinkets or which bears or contains any alcohol or nonnutritive article or substance except harmless coloring, harmless flavoring, harmless resinous glaze not in excess of 0.4 per cent, natural gum, and pectin [sec. 402 (d)].

26. Specifically requires label declaration of artificial coloring, artificial flavoring and chemical preservatives in food but exempts butter, cheese and ice cream from this requirement as far as artificial coloring is concerned [sec. 403 (k)].

27. Requires labeling of special dietary food to inform purchasers fully of its vitamin, mineral and other dietary properties [sec. 403 (j)].

28. Provides for the promulgation of a definition and standard of identity and a reasonable standard of quality and fill of container for each food but exempts from this provision fresh and dried fruits and vegetables, except avocados, cantaloupes, citrus fruits and melons [sec. 401, sec. 403 (g), (h)]. Butter is also exempt from this provision, but the act preserves the statutory definition and standard of identity for butter which became law in 1923 [sec. 902 (a)]. (The old law contains no authority for the establishment of definitions and standards of identity, and the authority to establish standards of quality and fill of container is limited to canned foods.)

29. Requires the labeling of food for which no definition and standard of identity has been fixed to disclose the ingredients by name, except spices, colorings and flavorings, which may be declared simply as spices, colorings and flavorings. Authorizes regulations prescribing exemptions from this requirement when compliance is impracticable or results in deception or unfair competition [sec. 403 (i)].

30. Does not contain the "distinctive name" joker of the old law under which any mixture or compound of food not injurious to health could escape control.

31. Provides increased criminal penalties for violations [sec. 303].

32. Authorizes the federal courts to restrain violations by injunction [sec. 302].

### EFFECT ON PRACTICE OF MEDICINE

How the new act will affect the practice of medicine is a question that has been asked by many physicians. While it is impossible to forecast to what extent the new act will ultimately aid the physician in his function of preventing and treating disease, one of the fundamental purposes of the law is to safeguard the public health. It may be pertinent to mention a few of the ways in which the act is directed toward this end:

The sections proscribing dangerous drugs and devices and injurious cosmetics and effecting more stringent control over deleterious ingredients in foods should bring about a lower general incidence of poisoning from these sources. It may be anticipated that the provisions which require disclosure of the active ingredients of drugs, adequate directions for use and warnings will aid the public in making more intelligent purchase and use of drugs. Similarly, the physician will be in a position to know the nature of the medication taken by his patients. Of particular importance is the protection provided by the act against the marketing of new drugs which have not been adequately tested for safety. The enhanced safeguards against variations in the strength, quality and purity of drugs should be of particular interest to those who administer them. Likewise, the requirement that the labels of foods offered for special dietary use bear adequate information to inform the purchaser fully as to its value, for such use will enable physicians more accurately to evaluate and advise their patients concerning such foods.

Enforcement of the Food, Drug and Cosmetic Act was entrusted to the Food and Drug Administration of the Department of Agriculture. It is to be particularly noted that this act does not include within its scope jurisdiction over advertising. In a separate bill, the so-called Wheeler-Lea Act, passed March 21, 1938, Congress specifically delegated the regulation of advertising of foods, drugs, devices and cosmetics to the Federal Trade Commission. Meats and meat food products are exempt from the provisions of the Food, Drug and Cosmetic Act to the extent that the Federal Meat Inspection Act is applicable to these products. Likewise the application of the Virus, Serum and Toxin Act of 1902 is not affected, modified or superseded by the act under discussion.

### OTHER RESULTS

With the enactment of more effective regulation of foods, drugs, devices and cosmetics, the question of how this legislation will affect the work of the Council on Pharmacy and Chemistry, the Council on Foods, the Advisory Committee on Advertising of Cosmetics and Soaps of the American Medical Association and other similar groups has been raised. It has, in fact, been thoughtlessly intimated that the work of these councils would be in the main unnecessary. In a recent address, the Secretary of the Council on Pharmacy and Chem-

istry [1] pointed out the fallacies of such a concept. In his informal discussion of the topic he pointed out the respects in which the new Food, Drug and Cosmetic Act and the rules of the Council are similar in purpose, as well as the respects in which they differ in function. The protection of the public from adulterated, misbranded and dangerous drugs, devices, cosmetics and foods is a large and never ending task. It is fitting that groups such as the American Medical Association and the American Dental Association, which have an interest in public health and welfare, should participate in this work. In this as in other functions of a democratic form of government, public welfare is served best when there is a vigorous public interest and participation in the activities of government.

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# *Council on Pharmacy and Chemistry*

## REPORTS OF THE COUNCIL

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.

PAUL NICHOLAS LEECH, Secretary.

## SOBISMINOL MASS AND SOBISMINOL SOLUTION

During 1933, Hanzlik undertook to develop a soluble bismuth preparation intended for oral as well as intramuscular administration in the treatment of syphilis. A patent [1a] was applied for by Hanzlik in 1936, and later the three manufacturers noted herewith were licensed by the Board of Trustees of Stanford University of California, assignee of the patent. The product originally called "Sodium Bismuthate Soluble" [2] was submitted to the Council on Pharmacy and Chemistry in 1936 for consideration under the names "Sodobismol" (E. R. Squibb & Sons), "Sodium Bismuthate Soluble-Cutter" (Cutter Laboratories) and "Sodium Bismuthate Soluble" (Eli Lilly & Co.). Subsequently the term "Sobisminol" was decided on as a suitable nonproprietary designation by Hanzlik, the respective manufacturers and the Council.

After preliminary consideration, Hanzlik and the respective manufacturers were informed that there was insufficient confirmatory evidence to warrant action by the Council at that time.

Shortly thereafter, Hanzlik reported to the Council on a small series of patients: Twenty-five had received oral treatment and fifty had been treated by injection. He indicated that data had been obtained on the absorption and excretion of bismuth after oral administration of sobisminol mass to several patients and that estimation of bismuth had been made on several hundred weekly specimens of urine. Subsequent material which formed the basis of later publications by Hanzlik, Lehman and Richardson [2] and by Sollmann, Cole and Henderson [3] was also called to the attention of the Council. More recently, a number of articles have appeared in the literature furnishing evidence in confirmation and extension of the earlier work. The nature of this pharmacologic and clinical evidence is reviewed herewith.

### CHEMICAL AND PHYSICAL PROPERTIES

It has been noted by both the A. M. A. Chemical Laboratory and by Hanzlik and his co-workers [4] that sobisminol contains no free sodium bismuthate [5] but rather some unidentified bismuth complex. It has been stated that the bismuth of sobisminol remains in stable, anionic electronegative) form in solution.[3] Hanzlik, Lehman and Richardson [2] discuss the preparation of two forms: a semisolid for oral administration and a solution to be used for injection and oral administration. The composition of the products to be marketed is described later.

The semisolid to be used for oral administration, termed "sobisminol mass," is a complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of 2 Gm. of sodium bismuthate, 4 Gm. of *tri*isopropanolamine and 1 cc. of propylene glycol or similar ratio in larger amounts. Appropriate quantities of sodium bismuthate, *tri*isopropanolamine and propylene glycol are thoroughly mixed and gradually heated to about 80 C., at which temperature an exothermic reaction occurs. When cool, the resultant mass is thoroughly mixed, tested, assayed and, if satisfactory, filled into capsules. The bismuth content of the finished product approximates 19.7 per cent. According to tests in the A. M. A. Chemical Laboratory, Sobisminol mass occurs as a red-brown to chocolate-brown pasty semisolid. The mass possesses an odor resembling that of *tri*isopropanolamine and a bitter taste, with a sweetish, metallic after-taste. It is soluble in water and in alcohol, yielding a clear solution in either solvent. It is partially soluble in acetone, chloroform and ether. The *p*H of a solution of sobisminol mass, made by dissolving 1 Gm. in water sufficient to make a final volume of 10 cc., should not be above 11.9, as determined with a glass electrode.

The solution to be used for injection and oral administration termed "sobisminol solution" contains a complex organic bismuth product, the chemical nature of which has not been fully established. It is obtained by dissolving the products of the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol in a mixture of propylene glycol and water. Each cubic centimeter of sobisminol solution contains 0.5 cc. of propylene glycol, a part of which enters into a reaction with 0.03 Gm. of sodium bismuthate and 0.08 Gm. of *tri*isopropanolamine, the remainder being water. Requisite quantities of sodium bismuthate, *tri*isopropanolamine and a portion of the necessary propylene glycol are thoroughly mixed and allowed to react as in the preparation of sobisminol mass. The remainder of the propylene glycol and water sufficient to make the final volume are added when the reaction is complete. After mixing, the resultant solution is tested, assayed and filled into ampules containing 1 cc. and 2 cc., respectively, or bottles containing 50 cc. Each cubic centimeter of the final solution contains the equivalent of approximately 20 mg. of bismuth. Sobisminol solution occurs as a clear, dark brown-red mobile liquid. It possesses an odor resembling that of *tri*isopropanolamine and a sweet, mildly metallic, taste. It is miscible with an equal volume of water or alcohol, yielding a clear solution. The specific gravity of sobisminol solution closely approximates 1.065 and the *p*H of the solution should not be below 11.1 or above 11.5, as determined with a glass electrode.

Sobisminol mass may be stored in a refrigerator; it remains stable at 38 C. Aqueous solutions of the drug do not precipitate serum proteins and may be boiled alone or with equal parts of serum without precipitation. Neither sobisminol mass in 10 per cent aqueous solution nor sobisminol solution is precipitated on the addition of equal volumes of solutions of 0.1 per cent hydrochloric acid or 0.5 per cent sodium bicarbonate, but both are precipitated by strong acids or alkali.[2]

### PHARMACOLOGY

The pharmacologic effects of sobisminol mass and solution have been studied by Hanzlik and his co-workers.

#### ABSORPTION OF BISMUTH

Systemic absorption of sobisminol (mass or solution) in animals was demonstrated by determining toxic effects and fatalities with large doses,[6] by the rate of disappearance of bismuth compounds from sites of injections [7] and by their appearance in the urine after administration by all routes—intramuscular, gastric or oral.

The dissection of muscles of rats and guinea pigs receiving single and repeated therapeutic and fatal doses of sobisminol solution intramuscularly failed to reveal precipitates or depots of bismuth or its compounds in injected regions.[8] Chemical analyses of these muscles by a method recently described (sensitive to about 0.04 mg. of bismuth per hundred cubic centimeters [9]) indicated practically complete absorption at the end of one hour. Hanzlik and his associates [10] made quantitative studies of absorption of bismuth from the ligated stomachs and ligated loops of intestine of rabbits and white rats after injection of sobisminol solution. Although the number of results was not large enough to permit generalizations, approximately 50 per cent of the sobisminol solution placed into empty ligated intestine or stomach was found to be absorbed in from one to eight hours. A limit of bismuth absorption was reached at the end of from twenty to twenty-four hours, and in searching for the cause of the limit they found that there were relatively large quantities of bismuth in the intestinal or stomach wall.[11]

Absorption of sobisminol (mass or solution) in man, as evidenced in clinical studies, appears to be rapid and sufficient to maintain antisyphilitic levels of bismuth concentration in the body.[12] Moreover, x-ray examination of gluteal regions in patients each receiving adequate antisyphilitic therapy in the form of injections of sobisminol solution failed to reveal shadows.[2]

#### DISTRIBUTION OF BISMUTH

Studies of bismuth distribution [13] in the tissues have supplied further evidence of systemic absorption of sobisminol. Analysis of the kidneys,

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1. Leech, P. N.: Relation of the Food Drug and Cosmetic Act to the Work of the Council on Pharmacy and Chemistry and Manufacturing Pharmacy, read at the twenty-eighth annual meeting of the American Drug Manufacturers Association, Hot Springs, Va., May 1, 1939.

1a. Hanzlik, P. J., assignor to Board of Trustees of Stanford University of California: Antisyphilitic Preparation and Process of Manufacture, U. S. Patent Office, Pat. No. 2,125,561, Aug. 2, 1938.

2. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sodium Bismuthate Soluble, Am. J. Syph., Gonor. & Ven. Dis. **21:** 1 (Jan.) 1937.

3. Sollmann, Torald; Cole, Harold, and Henderson, Katherine: Clinical Excretion of Bismuth: V. Excretion of Sobisminol and Some Other Bismuth Preparations for Oral Administration, Arch. Dermat. & Syph. **37:** 993 (June) 1938.

4. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Clinical Excretion of Bismuth After Oral Administration of Sobisminol, Arch. Dermat. & Syph. **36:** 708 (Oct.) 1937.

5. Sodium bismuthate is such a "strong" oxidizing agent that it could not have existed in such a mixture as proposed without rapidly oxidizing the other substances present.

6. Hanzlik, Lehman and Richardson, footnotes 2 and 21.

7. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Intramuscular Injection of Sobisminol: Absorption and Distribution of Bismuth, J. Pharmacol. & Exper. Therap. **62:** 413 (April) 1938.

8. Hanzlik, Lehman and Richardson, footnotes 2 and 7.

9. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Rapid Clinical Method for the Estimation of Bismuth in Urine, Arch. Dermat. & Syph. **36:** 725 (Oct.) 1937.

10. Hanzlik and others, footnotes 2 and 11.

11. Hanzlik, P. J.; Lehman, A. J.; Richardson, A. P., and Van Winkle, W., Jr.: Gastrointestinal Administration of Sobisminol: Absorption, Distribution and Excretion of Bismuth, J. Pharmacol. & Exper. Therap. **62:** 54 (Jan.) 1938.

12. Hanzlik and others, footnotes 2, 4 and 20. Sollmann, Cole and Henderson.[3]

13. Sollmann, Torald, and Henderson, Katherine: Bismuth Studies: VII. Bismuth Distribution in Dogs Following Intramuscular Injection of a Single Dose of Various Bismuth Preparations, Am. J. Syph., Gonor. & Ven. Dis. **22:** 739 (Nov.) 1938. Hanzlik and others, footnotes 2, 7 and 11. Lehman and Dock.[22]

blood, liver and brain[11] of experimental animals receiving sobisminol solution by injection into ligated viscera and by gastric administration indicated the presence of bismuth compounds. However, only from 30 to 40 per cent of the animals showed it in the blood and muscles, and only about 15 per cent in the brain.[8] Naturally, the greatest quantities of bismuth were present in the kidneys, since bismuth is excreted through those organs.

Sustained intramusclar medication in animals resulted in consistently higher quantities of bismuth in all tissues; however, different tissues varied greatly from animal to animal on the same therapeutic regimen. The tissues analyzed may be arranged in descending order of bismuth content as follows: kidney, liver, muscle, blood and brain.[8] Following intensive therapeutic regimens, the bismuth content of the blood was generally of the order of 0.02 to 0.03 mg. per hundred cubic centimeters, and of the brain from a trace up to 0.05 mg. per hundred grams. The bismuth content of the liver was of the general order of about 0.03 to 0.06 mg. per hundred grams. Single doses yielded much smaller and inconstant concentrations, which were not discussed. Failure to find bismuth in the blood consistently was attributed to the time interval between injection of sobisminol solution and removal of tissues for analysis.

The ingestion of aqueous 0.1 to 0.3 per cent solutions of sobisminol mass by rabbits for periods of two to three months resulted in the appearance of bismuth always in the kidneys, livers and muscles and, in about one half of the animals, in the brains. Such oral administration of sobisminol solution was shown to produce a blood concentration of bismuth comparable to that after intramuscular injection.

The distribution of bismuth in man after treatment with sobisminol (mass or solution) is attested by antisyphilitic concentrations of bismuth in the blood[14] and urine[15] and by the finding of bismuth in cerebrospinal fluid.[10]

### EXCRETION OF BISMUTH

Gastric administration of sobisminol solution to nine rabbits receiving doses equivalent to single and multiple (three to twelve) therapeutic doses resulted in prompt, definite and sustained urinary excretion of bismuth,[2] beginning the day following administration and reaching a peak on about the fourth day after single doses and on the tenth and twenty-eighth days after from three to twelve doses, respectively. Quantities of about 0.3 mg. of bismuth excreted daily were common. The total amounts of bismuth excreted were about as follows: 0.075 per cent of a total of 48 mg. of bismuth per kilogram, administered as a single dose; 2 per cent of a total of 64 mg. per kilogram, in three doses in one week; 0.3 per cent of a total of 576 mg. per kilogram in one month.

Hanzlik, Lehman, Richardson and Van Winkle[11] found that a considerable portion of the bismuth of sobisminol (mass or solution) administered orally escapes with the feces. Considerable amounts of bismuth were unaccounted for and presumably retained in the body (partly in the intestinal wall), supposedly to be excreted gradually over long periods in small quantities which could not be estimated. Fecal elimination of bismuth appeared to decrease as the urinary excretion of bismuth increased, and vice versa.

Comparable results on urinary and fecal excretion of bismuth have been reported by Stratton,[17] who found, however, that fourteen daily gastric doses of sobisminol solution, each equivalent to 20 mg. of bismuth per kilogram of body weight, raised the total urinary excretion of bismuth to only about five times the amount excreted after a single dose, further demonstrating the limit of excretion.

Intramuscular injections of sobisminol solution resulted in greater urinary excretion of bismuth in both animals and human subjects than was obtained by oral administration.[2] In rabbits receiving single doses of 0.4 mg. of bismuth per kilogram, excretion of bismuth began promptly the next day, the peak being reached on the third day, the maximum daily excretion being about 0.15 mg. and the duration thirty-five days. The total excretion was 37 per cent of the total bismuth injected. After three such doses injected in one week, the peak occurred on the fifth day, the maximum daily amount of bismuth excreted being 0.5 mg., the duration being about twenty days and the total excretion 30 per cent of the total administered. After twelve such doses in one month, the peak was reached on the sixteenth day, the maximum daily amount being 0.6 mg., the duration fifty days and the total excretion 42 per cent of the total administered.

The excretion of bismuth after oral and intramuscular administration of sobisminol to man has been studied by several groups of investigators. Hanzlik and his co-workers[18] and, more recently, Sollmann, Cole and Henderson[3] have studied bismuth excretion after oral administration, while Hanzlik and his co-workers[16] have studied excretion after intramuscular injection of sobisminol.

Twelve complete observations on seven different persons lead Hanzlik, Lehman, Richardson and Van Winkle[4] to conclude that the oral administration of sobisminol mass and solution to man resulted in prompt and definite excretion of bismuth in the urine, although most of the bismuth was expelled in the feces. The daily excretion of bismuth in the urine, after oral administration of 1.2 or 1.8 Gm. of sobisminol mass, is comparable to that observed after intramuscular injection of soluble bismuth compounds and above that occurring after administration of the insoluble compounds. It was observed that the urinary excretion of bismuth was demonstrable one-half hour after oral administration. Such excretion was found to vary directly with the dose, to manifest a cumulative tendency and to outlast the period of administration. However, the total urinary bismuth was but a small portion of the total amount of sobisminol administered—about 0.3 per cent for doses of 1.2 or 1.8 Gm. Urinary excretion was usually retarded or reduced by the presence of food and varied considerably with the individual. The median daily contents of bismuth of 660 weekly specimens of urine of patients receiving sobisminol mass were found to be, roughly, a thousandth of the amount of bismuth administered daily.

Sollmann, Cole and Henderson,[3] in a study of urinary excretion of bismuth during clinical oral administration of sobisminol mass to patients, found that doses of three capsules and of nine capsules daily for three weeks gave curves for urinary excretion resembling closely in course and degree those given by intramuscular injection of the water soluble and oil soluble compounds. The rise of excretion at the beginning of treatment and the decline after its discontinuance were as prompt as with preparations for intramuscular use. The level of excretion for the lower dose ranked just below that for other preparations; that for the higher dose ranked just above them, its median total excretion being about twice the median excretion obtained by other methods. The dose, however, had to be considerably higher with oral than with intramuscular administration. The total urinary bismuth excreted amounts to about 0.5 per cent of the quantity administered.

Bismuth excretion, after clinical intramuscular injection of sobisminol solution, indicates a sustained circulation of bismuth compounds through the body.[19] Daily urinary excretion of bismuth compounds fluctuates considerably but excretion continues for long periods, e. g. twenty days after one dose, thirty-four days after three doses and about sixty-four days after twelve doses. Total excretion of bismuth was about 35 per cent of the dosage administered. Fecal excretion of bismuth varied daily but amounted to about one ninth of that in urine. From 60 to 70 per cent of the bismuth injected as sobisminol solution remained unaccounted for, as in the case of rabbits.[20]

### TOXICITY

The toxicity of sobisminol administered orally as sobisminol mass and intravenously or intramuscularly as sobisminol solution has been determined.[6] It has been stated that, on the whole, the toxicity of sobisminol, intravenously and intramuscularly, compares favorably with that of other water soluble bismuth compounds used in the treatment of syphilis.[6] Fatal intramuscular doses of sobisminol solution in milligrams of bismuth per kilogram of animal were 175 in white rats and 77 in rabbits. The 50 per cent mortality dose was 105 mg. of bismuth per kilogram for white rats.

Intravenous fatal doses of sobisminol solution in milligrams of bismuth per kilogram were found to be 17.5 in rats and 8.4 in rabbits.[2] The 50 per cent mortality dose was 14 in rats. Later it was concluded that the majority of white rats would die from intravenous injections of sobisminol solution equivalent to 8 mg. of bismuth per kilogram, and rabbits from doses equivalent to 4.2 mg. of bismuth per kilogram.[21]

Sobisminol solution was administered gastrically to 113 white rats, twenty-one rabbits, ten cats and ten dogs.[6] The fatal gastric dose in white rats was 24 cc. of sobisminol solution, or 504 mg. of bismuth per kilogram; in rabbits 17 cc., or 357 mg. of bismuth per kilogram; in cats and dogs about 140 mg. of bismuth per kilogram. The 50 per cent mortality doses in rats and rabbits were quite similar; i. e. from 14 to 14.8 cc. of sobisminol solution, or from 294 to 310.0 mg. of bismuth per kilogram. It was stated that the number of cats and dogs used was too small and the contributory effects of central nervous depressants too uncertain for accurate determination of the fatal doses.

Hanzlik and his co-workers[22] and Lehman and Dock[23] have investigated the effects of continued oral medication with sobisminol mass in animals. Dilutions of sobisminol mass corresponding to 0.2, 0.3 and 0.5 per cent and from 0.1 to 0.6 per cent were ingested by rats and rabbits, respectively. Aqueous 1 per cent solution of sobisminol mass was not taken voluntarily by rabbits.[2] With increase in concentration and total dosage of sobisminol mass, increased losses of body weight and reduction in food intake of rabbits was noted. These tendencies, however, were present to about the same degree in rabbits on a bismuth free mixture[24] of the other ingredients of sobisminol. Pathologic changes in the heart, liver and kidneys of some animals on both doses of sobisminol and bismuth free mixture were found to be negative or negligible.[7] Hyperemia and congestion of the alimentary tract were observed in animals receiving doses of sobisminol solutions or bismuth free mixture in doses of toxic strength.[2] Renal changes resembling those due to mercury in fatal doses resulted from like doses of sobisminol solutions; but only transient renal changes, unaccompanied by progressive alteration, were observed after smaller doses.

A study of the toxicity of the ingredients of sobisminol, other than the bismuth compound, indicated that any contribution of these ingredients alone to the toxicity of intravenous and intramuscular injections of sobisminol in animals must be practically negligible.[21] It should be noted, however, that considerations of the contribution of possible oxidation products produced in the preparation of sobisminol mass and sobisminol solution to the toxicity of the drug have not been published.

The nonbismuth constituents of sobisminol, dissolved in water and water alone, formed a blank test control on the results with sobisminol in animals living under otherwise similar conditions. Solutions containing 0.8 per cent *tri*isopropanolamine and 5 per cent propylene glycol had practically no demonstrable effects on growth, body weight and daily food consumption in rats, and the daily volume drunk approximated that of water in the controls.

It has been shown that continued voluntary drinking of 0.3 per cent sobisminol solution by growing rats does not lead to the alteration of bone growth.[23] Two pregnant rats, and later their offspring, were allowed to drink aqueous 0.3 per cent sobisminol intermittently. On examination, the gross and microscopic structure of the bones showed no differences from controls. Bismuth compounds were found in the bones, soft tissues and pooled urines of these animals. Such results with effective doses of sobisminol prompted the discontinuance of further experimentation in this direction.[23]

14. Hanzlik, Lehman and Richardson.[20] Meininger and Barnett.[25] Scholtz, McEachern and Wood.[26]

15. Hanzlik, Lehman and Richardson, footnotes 2 and 20. Sollmann, Cole and Henderson, footnotes 3 and 30. Meininger and Barnet.[25] Scholtz, McEachern and Wood.[26]

16. Hanzlik, Lehman and Richardson, footnotes 2 and 20.

17. Stratton, Ernest K.: The Absorption and Elimination of Bismuth Following Its Oral Administration to Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **22**: 728 (Nov.) 1938.

18. Hanzlik and others, footnotes 2 and 4.

19. Sollmann, Cole and Henderson.[3] Hanzlik, Lehman and Richardson.[20]

20. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Excretion of Bismuth After Intramuscular Injection of Sobisminol: Experimental and Clinical Results, J. Pharmacol. & Exper. Therap. **62**: 404 (April) 1938.

21. Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sobisminol: Toxicity, Tolerance and Irritation According to Different Channels of Administration, J. Pharmacol. & Exper. Therap. **62**: 372 (April) 1938.

22. Hanzlik and others, footnotes 2 and 24.

23. Lehman. A. J., and Dock, W.: Effects of Drinking Sobisminol on Skeletal Changes in Growing White Rats, J. Pharmacol. & Exper. Therap. **63**: 88 (May) 1938.

24. Hanzlik, P. J., and Lehman, A. J.: Continued Voluntary Drinking of Sobisminol: General Effects, J. Pharmacol. & Exper. Therap. **62**: 389 (April) 1938.

### SIDE EFFECTS

Occasional incidence of slight and local edema and hyperemia were noted by Hanzlik, Lehman and Richardson[21] after the injection of large or toxic doses of sobisminol solution in animals but not, however, after doses of therapeutic order. Pain was not apparent.

Evidence of local irritation, indicated by vomiting, was present in cats and dogs given large doses of sobisminol solution gastrically. Tolerance was stated to be good when antiemetic drugs were used to avoid expulsion. Rodents tolerated the solution without emesis and showed no evidences of intestinal irritation, i. e. no diarrhea or bloody stools.

Hanzlik, Lehman and Richardson[2] initially reported that, of a group of ninety-seven male and female patients receiving doses of 1 cc. of sobisminol solution intramuscularly, 61 per cent complained of transient stinging and burning for about ten minutes or less, 13 per cent of pain or soreness for one hour, and 26 per cent for from one to three days. The injection of similar doses of an aqueous solution containing about 50 per cent of propylene glycol and 8 per cent of *tri*isopropanolamine gave rise to a similar distribution of complaints, although less aching was apparent. A decrease in the number of such complaints in a group of 260 patients was noted after reduction of the *tri*isopropanolamine content of sobisminol to 5 per cent. Persistent soreness, swelling, abscesses, induration and similar evidences of irritation were not apparent, although some latent soreness was manifested occasionally.

With sobisminol mass, Meininger and Barnett[25] observed that 37 per cent of 192 patients showed some form of reaction, 65 per cent having mild gastric reactions. Patients taking the preparation during the first week noted symptoms of fulness, nausea and occasional vomiting. There were four cases of acute stomatitis, but these patients later were able to take the remedy. Occasionally patients would complain of severe burning sensations in the esophagus, particularly if they did not take liberal amounts of water with the preparation. No kidney damage was noted. Five patients were forced to stop the preparation because of severe gastrointestinal upsets and five were changed to other drugs because the preparations were not being taken.

Scholtz, McEachern and Wood[26] encountered difficulty from gastrointestinal intolerance in the oral treatment of ninety patients with three and later two capsules of sobisminol mass three times a day. Thirty patients experienced nausea and vomiting. There was bismuth "grip" in ten, anorexia in eleven and diarrhea in six. There were ten cases of stomatitis, which usually did not interfere, but three of these cases were so severe that it was necessary to stop the sobisminol capsules. Seven patients had a bismuth line. In this study also there was no evidence of renal intolerance for the use of the preparation. From the standpoint of prolonged therapy, thirty-eight received the drug for two months or more without interruption. Nine were unable to take more than four capsules a day. Five took the drug daily for more than a year without consequent symptoms. There seemed to be no tendency to cumulative toxic effects.

### ANTISYPHILITIC EFFECTS

Hanzlik[27] found that the curative effects of injections of sobisminol solution in experimental syphilis were apparently equal to those obtained by the use of other bismuth preparations. Clearing of organisms from lesions after single doses of 10, 20 and 30 mg. per kilogram occurred in twenty, seven and five days, respectively, and healing in thirty-five, sixteen and eleven days, respectively.

Clinical evidence of the antisyphilitic action of sobisminol mass and sobisminol solution has been reported by Hanzlik, Lehman and Richardson,[2] Sollmann, Cole, Henderson and others,[28] Meininger and Barnett,[25] Scholtz, McEachern and Wood,[26] and Kay and Fricke.[29]

Hanzlik, Lehman and Richardson[2] discussed preliminary results obtained with sobisminol solution in the clinical treatment of syphilis in all stages. The effects of sobisminol solution alone or in combination courses with arsenicals, administered by the intramuscular route, appeared to be equivalent to the effects with other bismuth products alone or with arsenicals. Oral administration of sobisminol mass resulted in the rapid clearing of lesions in secondary and tertiary syphilis. It should be noted, however, that these authors concluded that none of the patients had been followed long enough clinically for an adequate evaluation of the drug.

Sollmann, Cole and Henderson[30] have suggested combination courses of sobisminol solution and bismuth subsalicylate in oil as a means of obtaining an initial high concentration of bismuth in the treatment of patients with acute syphilis who are sensitive to arsenicals. Two series of three patients each, on iodobismitol with saligenin and sobisminol, respectively, were given three injections of the preparations the first week, two injections the second week and one injection the third week. The median urinary excretion curve of the series on sobisminol was shown to have a higher urinary bismuth excretion than the series on iodobismitol with saligenin and also a more prolonged excretion after the injections had ceased. Moreover, when the two preparations were used respectively in conjunction with intramuscular injections of bismuth subsalicylate in oil it was found that the median urinary bismuth excretion in a series of patients on sobisminol and bismuth subsalicylate in oil showed a higher and more prolonged excretion than a like series of patients on iodobismitol with saligenin and bismuth subsalicylate in oil.

Sollmann, Cole and Henderson[3] also administered three capsules equivalent to 420 mg. of bismuth, three times a day to three patients with primary and two with secondary syphilis. Spirochetes disappeared from lesions in a median of seven days. Moreover, excretion of bismuth after oral administration of sobisminol capsules was found to be higher than after administration of most bismuth preparations by any route.

Scholtz, McEachern and Wood[26] at first administered three capsules of sobisminol three times a day, later reducing the dose to two capsules three times a day, in a series of eighty cases of various types of syphilis. In cases of early syphilis, sobisminol mass was never used for more than two weeks without use of arsenicals. In five cases of seropositive primary syphilis, dark fields were negative in a median of five days, with extremes of two and eight days. Lesions became involuted in a median of fourteen days, with extremes of ten and twenty. In twenty-seven cases of secondary syphilis the lesions of twenty-two were completely involuted in an average of twelve days, the lesions of ten patients taking two capsules three times a day were completely involuted in about thirteen days, and of twelve patients taking three capsules three times a day, in about twelve days. The small advantage of the larger dose was, however, counterbalanced by the lack of gastrointestinal symptoms when the smaller dose was used. The tertiary lesions of six patients involuted in thirty-one days, and squamous palmar lesions in thirty-three days. A large gumma of the soft palate disappeared in twenty days. These authors also believed that sobisminol would eventually prove to be of value in syphilis of the central nervous system. One important point that is brought out is the evidence of sustained therapeutic effects from the drug when it is administered orally. If, however, treatment with sobisminol mass by mouth is stopped, the antisyphilitic effect appears to stop. In two cases of secondary syphilis, complete involution occurred in about two weeks. Because of nonattendance, the patients were not placed on arsenical treatment and it was noted that reactivation and relapse of the processes occurred within a period of two or three weeks.

Meininger and Barnett[25] noted that the disappearance of spirochetes in twenty-nine cases of primary syphilis usually occurred in about four days when three capsules of sobisminol mass three times a day were being taken. In four other cases they were still present at the end of fourteen days, at which time arsenical therapy was instituted. Primary syphilitic lesions involuted in an average of about ten days. Secondary lesions involuted in about the same length of time in twenty-six cases, while eleven additional cases of secondary syphilis were not entirely free at the end of fourteen days when neoarsphenamine was started. The late lesions of syphilis required about 4.5 weeks of treatment with sobisminol capsules before involution occurred. Treatment with sobisminol capsules alone was continued for an average of about five months with seventy-three patients having late syphilis, more than six months with twenty-three patients, and more than twelve months with seven patients. Serologic reversal was noted in three cases: one reversed at four months, one at seven months and one was 2 plus when treatment was stopped at the end of ten months, becoming negative three months later.

Ninety-three of their patients were treated with sobisminol mass in a form of combination course with neoarsphenamine similar to that described by Beckh and Barnett[31] for iodobismitol with saligenin. A comparison of the results obtained by this method in thirty-six patients in the primary stage of syphilis, with fifty-eight patients on neoarsphenamine and iodobismitol with saligenin, indicated that sobisminol was superior in the production of serologic reversal and in the prevention of nerve involvement. Relapse was noted, however, in 12 per cent of the sobisminol-neoarsphenamine group and in 11 per cent of the iodobismitol with saligenin group. Relapses were clinical in type in eight of the first group and four of the second group, serologic only in one of the first group and five of the second group. The average time of the occurrence of relapse in the first group was fourteen months and in the second group eighteen months. The authors stated that the patients in the sobisminol group were still in the potential relapse period and more were to be expected. Only seventeen of the sobisminol group had been followed for eighteen months; two had already relapsed. These authors believe, however, that if the period of observation for the sobisminol group had been longer it would compare less favorably with iodobismitol with saligenin in the prevention of relapse. They express the opinion that the occurrence of relapse in the two groups may be related to the treatment patterns that were used.

Kay and Fricke[29] have reported the use of sobisminol mass in five cases of late syphilis, in four of which they used a dosage of one capsule three times a day until from 300 to 1,200 capsules (from 70 to 166 Gm. of bismuth) were employed. Symptomatic and serologic improvement appeared in all four patients. Tolerance was found to be good, and, in spite of the length of the period of treatment, serious reactions were rare.

### COMMENT

In view of the evidence, it would appear that sobisminol solution administered by the intramuscular route (*a*) exerts a definite antisyphilitic effect in experimental syphilis in the rabbit in doses of about 5 mg. per kilogram of body weight; (*b*) exerts a definite curative effect in experimental syphilis in the rabbit in a minimum curative dose of about 7 mg. per kilogram of body weight; (*c*) causes the disappearance of Spirochaeta pallida from chancres and condylomas of human beings in a period of from four to seven days; (*d*) acts to clear primary syphiloderms in about ten days, secondary syphilitic lesions in an average of about fourteen days, and tertiary syphilitic lesions in about thirty days; (*e*) acts satisfactorily in causing the reversal of the positive serologic blood reaction; (*f*) is moderately well tolerated after local injection; (*g*) produces a urinary excretion of bismuth as high as or higher than any other bismuth compound now employed in the treatment of syphilis, and (*h*) is followed by no greater incidence of relapse than after administration of other bismuth compounds. From the foregoing it is apparent that sobisminol solution offers a means of obtaining, by injection treatment, the systemic effects of bismuth in the treatment of syphilis.

In evaluating a bismuth compound which is to be administered orally, there are certain disadvantages which must be considered. Thus, with sobisminol mass a large number of the patients have gastrointestinal upsets, occasionally severe enough

25. Meininger, W. M., and Barnett, C. W.: The Treatment of Syphilis with Sobisminol Mass Given by Mouth, this issue, p. 2214.
26. Scholtz, J. R.,; McEachern, Katherine D., and Wood, Clyde: Sobisminol Mass Clinical Results with Oral Administration, this issue, p. 2219.
27. Hanzlik, P. J.: Sodium Bismuthate Soluble in Experimental Syphilis, J. Pharmacol. & Exper. Therap. **59**: 328 (March) 1937. Hanzlik, Lehman and Richardson.[2]
28. Sollmann, Cole and Henderson, footnotes 3 and 30.
29. Kay, Willard E., and Fricke, John W.: Sobisminol: Its Oral Administration, California & West. Med. **50**: 348 (May) 1939.
30. Sollmann, Torald; Cole, Harold, and Henderson, Katherine: Combination Courses of Bismuth Administration, J. A. M. A. **111**: 2175 (Dec.) 1938.
31. Beckh, Walter, and Barnett, C. W.: The Effect in Early Syphilis of Combined Treatment in Comparison with Alternating Treatment, Arch. Int. Med. **63**: 974 (May) 1939.

to cause discontinuance of the drug;[32] bismuth stomatitis is seen occasionally;[32] a bismuth line is not rare.[26] There appears to be a tendency for some individuals to neglect their treatment as soon as they begin to feel better. Some of the patients examined by Meininger and Barnett[25] were found to have no bismuth in the urine, but it is believed that they were patients who had neglected the treatment. When injections are being given at stated intervals, the patient arranges for this treatment, knows when he is due for it and usually appears. On the other hand, if he is simply given some capsules to take, he may forget to take them or he may leave them at home and in that way be negligent in their use. Moreover, because of gastrointestinal intolerance the patient may become discouraged in the early stages of his syphilis at a time when treatment is most necessary. These factors acquire greater significance when it is considered that no sustained bismuth effect is derived from the use of sobisminol capsules, judging by the rapid drop of urinary bismuth excretion as soon as the capsules are stopped.[30] It is not surprising, therefore, that Scholtz, McEachern and Wood[26] noted two cases of relapse in early syphilis within two weeks after sobisminol capsules were stopped. Meininger and Barnett[25] also speak of this danger.

The relapse tendency when oral bismuth as a medication is employed is unfortunate, because it is in the first stages of syphilis that the relapses are most frequently seen. If a bismuth preparation is employed which allows the antisyphilitic effect to cease soon after its administration is stopped, with no bismuth depots in the body, there is more danger of relapse than when continuous bismuth injections are carried out.

Finally, there is danger of self medication from the use of sobisminol mass. In such case an individual, unaware of the true character of the syphilis, may use sobisminol mass for a time, perhaps not in the proper dose, until he feels better, and then stop further treatment. As a result, an early infectious relapse and the consequent spread of the disease to other persons might occur.

It must be noted that the administration of sobisminol mass in capsules by the oral route[2] (*a*) results in an effect comparable to sobisminol injection therapy in sterilizing syphilis in rabbits and in destroying organisms in local chancres; (*b*) produces rapidly, in a dose of three capsules three times a day, a high urinary bismuth excretion, comparable to that of any other bismuth compound studied thus far; (*c*) causes primary syphiloderms to clear in about ten days, secondary lesions in about fourteen days and tertiary lesions in about thirty days; (*d*) results in satisfactory action in reversing positive serologic tests, and (*e*) exerts a definite action in the treatment of syphilis, clearing chancres and condylomas.

There is a definite place for oral therapy with sobisminol mass in the treatment of syphilis, although probably not so much in the early stages as in the latent period or in the later stages of the disease. It should be useful in certain early cases of syphilis to provide continuity when conditions necessitate the patient's being absent from the physician for a matter of a week or more. It is suggested, however, that intramuscular therapy is preferable in all early syphilis, if it is possible, for the purpose of maintaining continuous therapy, if for no other reason. Attention is directed to the fact that no bismuth depot is established when the product is administered solely by the oral route. From the experimental and clinical evidence described, it must be noted that the last course of bismuth therapy should be given as a series of insoluble injections, in order to establish bismuth depots for continuation of sustained bismuth effects.

The product has been before the Council on Pharmacy and Chemistry for approximately three years, during which time there was much consideration given by all concerned. The Council appreciated the cooperation of Dr. Hanzlik and his group and their decision not to permit commercial promotion of the product unless it was accepted by the Council. Three firms have submitted the product and have agreed to market it in conformance to the rules of license laid down jointly by the board of trustees and the department of pharmacology of Stanford University and with the rules of the Council.

32. Meininger and Barnett.[25] Scholtz, McEachern and Wood.[26]

The Council voted to include Sobisminol Solution and Sobisminol Mass in New and Nonofficial Remedies with the understanding, in the case of the latter, that all precautions will be taken against its use for self medication,[33] and also voted to accept brands of the product.

## NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

PAUL NICHOLAS LEECH, Secretary.

**SOBISMINOL MASS.**—A complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol. It contains between 19.25 and 20.25 per cent of bismuth.

*Actions and Uses.*—Sobisminol mass is proposed in the treatment of syphilis and is intended for use by the oral route. It is particularly indicated for those patients unable to undergo intramuscular bismuth therapy and to supplant therapy by that route for patients compelled for a time to be out of contact with their physician. Again it may be indicated in certain other types of syphilis, e. g. congenital and latent syphilis. It is to be emphasized that it is too dangerous a drug to be employed by the patient without the careful supervision and direction of his physician, and it is sold only on prescription. In the first few days of therapy the patient should be carefully supervised and later watched for evidence of gastrointestinal upsets and of bismuth intoxication.

*Dosage.*—Adult dosage, from two to three capsules three times a day, taken with plenty of water, at 10 a. m., 3 p. m. and 8 p. m. Each capsule represents 150 mg. of metallic bismuth. Unless contraindications arise, such therapy may be continued for from ten to twelve weeks and represents a course of bismuth therapy. For children the dosage may be cut down to one capsule three times a day, or a 75 mg. capsule three times a day for a young child.

Sobisminol mass occurs as a red-brown to chocolate-brown colored pasty mass, possessing an odor similar to *tri*isopropanolamine and a bitter taste, with a sweetish, metallic after-taste. It is soluble in water and alcohol, partially soluble in ether and acetone. The *p*H of a solution made by dissolving 1 Gm. of sobisminol mass in sufficient distilled water to make a volume of 10 cc. should not be above 11.9 as determined with a glass electrode.

Dissolve 1 Gm. of sobisminol mass in 10 cc. of water and halve the solution; to one portion add 5 cc. of 0.5 per cent sodium bicarbonate solution; to the other portion add 5 cc. of 0.1 per cent hydrochloric acid: neither solution yields a precipitate within fifteen minutes.

Dissolve 2 Gm. of sobisminol mass in 100 cc. of water; boil a 5 cc. portion: the solution remains clear and unchanged. To a separate portion of 1 cc. add 10 cc. of water and 1 cc. of 5 per cent sodium iodide solution: the solution remains clear. To another 1 cc. portion add 1 cc. of diluted hydrochloric acid, 5 cc. of water and 5 cc. of hydrogen sulfide solution: a black precipitate forms; to another 1 cc. portion add 3 cc. of diluted sulfuric acid and 1 cc. of 5 per cent sodium iodide solution: a red precipitate forms. To a 20 cc. portion add 2 cc. of nitric acid, adding more nitric acid dropwise, if necessary, until the solution is clear; divide into two equal parts; retain one part as a control and add 2 cc. of silver nitrate solution to the other part: when compared with the control, not more than a trace of turbidity is apparent *(chloride)*. To another 20 cc. portion add 2 cc. of hydrochloric acid, adding more hydrochloric acid dropwise, if necessary, until the solution is clear; divide into two equal parts, retain one part as a control and add 2 cc. of barium chloride solution to the other part: when compared with the control, not more than a trace of turbidity is apparent *(sulfate)*.

Transfer about 5.0 Gm. of sobisminol mass, accurately weighed, to a 100 cc. volumetric flask, add water to the mark and shake the contents thoroughly. Determine the nitrogen content of an accurately measured 10 cc. portion according to the method described in Methods of Analysis of the Association of Official Agricultural Chemists, fourth edition, p. 24, articles 22 and 23. In the procedure add 0.1 Gm. of anhydrous copper sulfate and continue the digestion for a period of two and one-half hours after the solution becomes clear: The amount of nitrogen is not less than 3.60 per cent nor more than 4.40 per cent.

Dissolve about 0.6 Gm. of sobisminol mass, accurately weighed, in 100 cc. of water and rapidly add 8 cc. of concentrated nitric acid. Add

33. In this connection it may be pointed out that the licensees have made the following agreement with Stanford University:

"Neither Licensee nor his agents, in carrying out the sale and distribution of said products shall:

(*a*) Furnish to retailers or condone or encourage use by retailers of any counter advertising or counter displays of said products;

(*b*) Advertise said products directly to the public by advertisements in magazines or newspapers of general circulation or by printed circulars distributed to the general public;

(*c*) Condone or encourage in any way 'over the counter' sales of said products to the public except through licensed pharmacists or prescriptions of licensed physicians.

Licensee shall use its best efforts to maintain distribution of said products exclusively through licensed pharmacists on prescription of licensed physicians, and to prevent over the counter sales of said product to the public."

two drops of methyl red solution and then add ammonia water until the solution just turns yellow; add 3 cc. of nitric acid, heat to boiling and slowly add, with cautious stirring, 50 cc. of 10 per cent *diammonium* phosphate solution; dilute to a volume of about 400 cc. with boiling water and allow the mixture to stand for one hour at 80 C. Collect the precipitate on a tared Gooch crucible by first filtering the supernatant liquid, then wash the precipitate by decantation with four 50 cc. portions of hot water, passing these washings through the crucible, and finally complete the transfer of the precipitate by means of cold water; dry the crucible and contents at 110 C. for one hour, suspend the crucible within another crucible and ignite gently for forty-five minutes, adjusting the flame so that the bottom of the lower crucible is heated to dull redness; cool the crucible and contents and weigh the ignited material as bismuth phosphate; use the factor 0.6875 for the conversion of bismuth phosphate to bismuth: the amount of bismuth found corresponds to not less than 19.25 per cent nor more than 20.25 per cent.

*Propylene Glycol:* The propylene glycol used in the preparation of sobisminol mass and sobisminol solution conforms to the New and Nonofficial Remedies standards for this substance, which see.

*Sodium Bismuthate:* The sodium bismuthate used in the preparation of sobisminol mass and sobisminol solution conforms to the following tests for identity and purity:

Sodium bismuthate occurs as a nearly odorless, yellow-brown powder containing not less than 80 per cent of $NaBiO_3$.

Dissolve 1 Gm. of sodium bismuthate in a mixture of 5 cc. of hydrochloric acid and 15 cc. of water: a slightly turbid, yellow solution results. Agitate 2 Gm. of sodium bismuthate with 50 cc. of water frequently during one hour: the resultant suspension is alkaline to phenolphthalein; filter, rejecting the first few cubic centimeters; evaporate 25 cc. of the clear filtrate in a tared dish, dry the residue at 120 C. and weigh: the weight of the residue is not more than 0.003 Gm.

Boil 2.5 Gm. of sodium bismuthate and 40 cc. of water for ten minutes, cool, dilute to 50 cc. with water, mix well, filter and divide into 10 cc. portions; to one portion add 0.5 cc. of nitric acid and 1 cc. of silver nitrate solution: the turbidity should not be greater than that produced in a control containing 0.025 mg. of chloride ion *(chloride)*; to another portion add 0.5 cc. of normal hydrochloric acid, filter, if necessary, and add to the clear filtrate 1 cc. of barium chloride solution: the turbidity should not be greater than that produced in a control containing 0.05 mg. of sulfate ion *(sulfate)*.

Heat 0.5 Gm. of sodium bismuthate with 3 cc. of sulfuric acid until fumes of sulfur trioxide appear, then complete the test for arsenic according to the method described in the U. S. P. XI: The arsenic content should not exceed 2 parts per million.

Dissolve about 0.25 Gm. of sodium bismuthate, accurately weighed, in 8 cc. of nitric acid, dilute with 100 cc. of water and continue the assay for bismuth as directed under sobisminol mass: the amount of bismuth found corresponds to not less than 66.5 per cent nor more than 72.5 per cent.

Transfer about 0.7 Gm. of sodium bismuthate, accurately weighed, to a flask and add 25 cc. of acid ferrous sulfate solution, stopper the flask, allow it to stand one-half hour with frequent shaking, and titrate the excess ferrous sulfate with 0.1 normal potassium permanganate solution: the sodium bismuthate should not be less than 80 per cent $NaBiO_3$. (The acid ferrous sulfate solution must be freshly prepared and standardized by a control titration).

*Triisopropanolamine:* The *tri*isopropanolamine, $N(C_3H_6OH)_3$, used in the preparation of sobisminol mass and sobisminol solution responds to the following tests for identity and purity:

*Tri*isopropanolamine occurs as a colorless to pale yellow colored, pasty semicrystalline mass, possessing a slight characteristic odor and a bitter taste. It melts to a clear liquid at a temperature of not less than 46 C. *Tri*isopropanolamine is readily soluble in acetone, alcohol, ether, chloroform and water.

Dissolve 1 Gm. of *tri*isopropanolamine in 10 cc. of water: the solution is alkaline to litmus and only very slightly turbid. Dissolve 1 Gm. of *tri*isopropanolamine in 20 cc. of water, divide the solution into two portions; to one portion add 0.5 cc. normal hydrochloric acid, filter, if necessary, and add to the clear filtrate 1 cc. of barium chloride solution: not more than a faint turbidity develops in five minutes *(sulfate)*; to the other portion add 0.5 cc. of nitric acid and 1 cc. of silver nitrate solution: not more than a faint turbidity is produced *(chloride)*.

The arsenic content of *tri*isopropanolamine is not more than 2 parts per million; heavy metals are absent (U. S. P. XI). Incinerate 5 Gm. of *tri*isopropanolamine: the weight of the ash does not exceed 0.05 per cent.

Transfer about 5 Gm. of *tri*isopropanolamine to a 100 cc. volumetric flask and assay for nitrogen as directed under sobisminol mass: the amount of nitrogen found is not less than 7.1 per cent nor more than 7.6 per cent. Dissolve about 1 Gm. of *tri*isopropanolamine, accurately weighed, in 50 cc. of distilled water and titrate with half-normal hydrochloric acid; each cubic centimeter of which is equivalent to 0.0955 Gm. of *tri*isopropanolamine, using methyl red as the indicator: the *tri*isopropanolamine content should be not less than 98.5 per cent nor more than 101.5 per cent.

**Sobisminol Mass-Cutter.**—A brand of sobisminol mass-N. N. R.

Manufactured by Cutter Laboratories, Berkeley, Calif., by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938; expires 1955). No U. S. trademark.

*Sobisminol Mass-Cutter Capsules:* Each capsule contains 0.75 Gm. of sobisminol mass representing 150 mg. of bismuth as an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

**Sobisminol Mass-Lilly.**—A brand of sobisminol mass-N. N. R.

Manufactured by Eli Lilly and Company, Indianapolis, by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938; expires 1955). No U. S. trademark.

*Pulvules Sobisminol Mass-Lilly:* Each pulvule contains 0.75 Gm. of sobisminol mass representing 150 mg. of bismuth as an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

**Sobisminol Mass-Squibb.**—A brand of sobisminol mass-N. N. R.

Manufactured by E. R. Squibb & Sons, New York, by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938; expires 1955). No U. S. trademark.

*Sobisminol Mass-Squibb Capsules:* Each capsule contains 0.75 Gm. of sobisminol mass representing 150 mg. of bismuth as an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

**SOBISMINOL SOLUTION.**—A solution containing a complex organic bismuth product the chemical nature of which has not been fully established. It is obtained by dissolving the products of the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol in a mixture of propylene glycol and water. Each cubic centimeter of the solution contains between 19.5 and 20.5 mg. of bismuth and 0.5 cc. of propylene glycol.

*Actions and Uses.*—Sobisminol solution is proposed in the treatment of all types of syphilis and is claimed to be free from unusual discomfort when used by the intramuscular injection route.

*Dosage.*—From 1 to 2 cc. intramuscularly into the muscles of the buttocks twice a week. With young children the dosage may be lowered in proportion. Generally a series of from twenty to twenty-five injections is considered a course of treatment. In cases of arsenical sensitization the bismuth injections may be continued for a much longer period.

Sobisminol solution occurs as a clear, dark brown-red colored liquid, possessing an odor similar to *tri*isopropanolamine and a sweet, mildly metallic taste. It is miscible with an equal volume of water or alcohol.

The *p*H of a portion of sobisminol solution is not below 11.1 nor above 11.5 as determined by means of a glass electrode. The specific gravity of sobisminol solution is not less than 1.064 nor more than 1.066 at 25 C.

Undiluted sobisminol solution responds to the tests for identity and purity stated under sobisminol mass.

Transfer 5 cc. of sobisminol solution, accurately measured, to a 500 cc. beaker and determine the bismuth content according to the method stated under sobisminol mass: the amount of bismuth found is not less than 0.0195 Gm. nor more than 0.0205 Gm. per cubic centimeter.

Transfer 5 cc. of sobisminol solution, accurately measured, to a 500 cc. Kjeldahl flask and determine the nitrogen content according to the method stated under sobisminol mass: the amount of nitrogen found is not less than 0.0054 Gm. nor more than 0.0060 Gm. per cubic centimeter.

The propylene glycol, sodium bismuthate and *tri*isopropanolamine used in the preparation of sobisminol solution corresponds to the standards for these substances as indicated under sobisminol mass.

**Sobisminol Solution-Cutter.**—A brand of sobisminol solution-N. N. R.

Manufactured by Cutter Laboratories, Berkeley, Calif., by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938; expires 1955). No U. S. trademark.

*Sobisminol Solution-Cutter, Ampoules 1 cc.:* Each ampule contains 20 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

*Sobisminol Solution-Cutter, Ampoules 2 cc.:* Each ampule contains 40 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

**Sobisminol Solution-Lilly.**—A brand of sobisminol solution-N. N. R.

Manufactured by Eli Lilly and Company, Indianapolis, by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938; expires 1955). No U. S. trademark.

*Sobisminol Solution-Lilly, Ampoules 1 cc.:* Each ampule contains 20 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

*Sobisminol Solution-Lilly, Ampoules 2 cc.:* Each ampule contains 40 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

*Sobisminol Solution-Lilly, Ampoules 50 cc.:* Each cubic centimeter contains 20 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

**Sobisminol Solution-Squibb.**—A brand of sobisminol solution-N. N. R.

Manufactured by E. R. Squibb & Sons, New York, by license of Stanford University under U. S. patent 2,125,561 (Aug. 2, 1938; expires 1955). No U. S. trademark.

*Sobisminol Solution-Squibb, Ampuls 1 cc.:* Each ampule contains 20 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

*Sobisminol Solution-Squibb, Ampuls 2 cc.:* Each ampule contains 40 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

*Sobisminol Solution-Squibb, Ampuls 50 cc.:* Each cubic centimeter contains 20 mg. of bismuth in the form of an aqueous solution containing approximately 50 per cent of propylene glycol and an organic bismuth compound obtained by the interaction of sodium bismuthate, *tri*isopropanolamine and propylene glycol.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, DECEMBER 16, 1939

## The Platform of the American Medical Association

The American Medical Association advocates:

1. The establishment of an agency of the federal government under which shall be coordinated and administered all medical and health functions of the federal government exclusive of those of the Army and Navy.

2. The allotment of such funds as the Congress may make available to any state in actual need, for the prevention of disease, the promotion of health and the care of the sick on proof of such need.

3. The principle that the care of the public health and the provision of medical service to the sick is primarily a local responsibility.

4. The development of a mechanism for meeting the needs of expansion of preventive medical services with local determination of needs and local control of administration.

5. The extension of medical care for the indigent and the medically indigent with local determination of needs and local control of administration.

6. In the extension of medical services to all the people, the utmost utilization of qualified medical and hospital facilities already established.

7. The continued development of the private practice of medicine, subject to such changes as may be necessary to maintain the quality of medical services and to increase their availability.

8. Expansion of public health and medical services consistent with the American system of democracy.

## ORAL BISMUTH THERAPY IN SYPHILIS

The use of alternating courses of arsenicals, administered intravenously, with intramuscular injections of bismuth compounds in the treatment of syphilis is a standard procedure with many syphilologists. With this therapy the disease is under constant attack by the respective metallic compounds. Physicians who use the injection technic may be assured that the patient has received the prescribed dose. The routine weekly schedule facilitates the observation of the effect of the medication on the disease and on the patient. Regularity of examination and treatment is important to both the patient and the physician. It affords frequent opportunity for mental and moral influence, and encouragement by the physician. It aids in the maintenance of adequate records, which are useful in statistical evaluation of various therapeutic regimens. Perhaps most important to the individual and to society, routine administration of medication provides the physician with an effective means of insuring the prolonged cooperation of the patient—an essential requirement for the successful termination or control of the disease. Any plan of treatment which lacks these advantages requires serious consideration from a public health and socio-economic point of view before it is accepted as a suitable method for the treatment of syphilis.

Now, for the first time, appears a metallic preparation which seems to be useful when administered orally for the treatment of syphilis. The fact that it is taken orally indicates that it may frequently be adapted for self administration. This form of therapy is certainly not advisable except for intelligent, cooperative patients. Forgotten doses of medication or negligent behavior on the part of the patient must inevitably lead to relapse with consequent possibilities of infection of other people. It is essential that the patient take the medication regularly, as directed by the physician, or that the physician insist on the intramuscular route for therapy for uncooperative patients.

There are, of course, certain instances in which the oral route of medication would be a valuable adjunct in syphilis therapy. It can be used with caution for those individuals whose business or profession necessitates occasional absences from the physician's supervision. It should prove useful for those rare persons who have unusual difficulty in taking intramuscular injections because of resultant pain and induration of the muscles. It is also possible that in selected cases of congenital syphilis and in some cases of cardiovascular and latent syphilis the oral route of medication would be distinctly useful.

In the course of experiments directed toward the utilization of sodium bismuthate in antisyphilitic therapy, Hanzlik, at Stanford University, evolved preparations resulting from the interaction of sodium bismuthate, tri-isopropanolamine and propylene glycol, known as sobisminol mass and sobisminol solution. These products have been before the Council on

Pharmacy and Chemistry for approximately three years, a period which was necessary for the accumulation and proper evaluation of evidence for the efficacy of the orally administered product. Elsewhere in this issue of THE JOURNAL appears a statement by the Council on Pharmacy and Chemistry on sobisminol mass in capsules and sobisminol solution, and the announcement of acceptance of various marketed brands of these products. The studies of Hanzlik and his co-workers, of Sollmann, Cole and Henderson, and of others have shown, by clinical observations of antisyphilitic effects of sobisminol mass when given in sufficient dosage, that there is satisfactory absorption of bismuth following sobisminol mass by the oral route. Similarly confirmatory studies by Meininger and Barnett and by Scholtz, McEachern and Wood appear in this issue (pp. 2214-2223). Attention is directed to a rapid clinical method for quantitative determination of bismuth, devised by Hanzlik and his co-workers, which has been used effectively to maintain accurate observations of the level of bismuth excreted in the urine of patients treated with bismuth preparations. Adequate references to these studies appear in the report of the Council on Sobisminol (this issue, p. 2235). While some gastrointestinal disturbances have been encountered, generally they have not been sufficiently serious to interfere with adequate treatment.

This oral remedy cannot be expected to replace completely the carefully supervised use of other established therapeutic agents. It is to be emphasized that, while an oral bismuth preparation may in some situations be substituted in whole or in part for a bismuth preparation administered intramuscularly, it could never serve as an adequate substitute for alternate courses of arsenicals and bismuth compounds.

Sobisminol mass must not be sold over the counter to the public as a cure for syphilis. If it were thus marketed, the product would be a real danger and detriment to the public health. Both Hanzlik and the manufacturers are most anxious that no such contingency shall arise. Therefore, according to agreements between the board of trustees of Stanford University and each of the three firms already licensed to manufacture the product, every legal effort is being made to prevent the sale of capsules of sobisminol mass to the public other than on or by the prescription of the physician. Self medication in acute syphilis can only lead to relapse and resultant danger to the public health.

The ultimate evaluation of the therapeutic efficacy of a new drug such as sobisminol mass necessarily requires a long time. The close cooperation of Hanzlik and other investigators, the manufacturers, the Food and Drug Administration and the Council on Pharmacy and Chemistry in careful studies designed to evaluate and control this new product properly is highly commendable.

To summarize: A new antisyphilitic agent with the special property of effective oral administration will soon be taking its place in the alleviation of the ravages of syphilis. Physicians, pharmacists and public health authorities must take care that sobisminol mass is not supplied directly to the public. Such distribution would obviously result in inadequate treatment of unrecorded and uncontrolled cases and thus would become a serious menace both to the individual and to the public health. Lastly it is pointed out that oral administration of bismuth compounds is not intended to replace the generally accepted use of bismuth preparations intramuscularly, except where special conditions prevail.

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## COLLAPSE THERAPY FOR PULMONARY TUBERCULOSIS AS A PUBLIC HEALTH MEASURE

Since the late Theodore B. Sachs called attention to the menace of the wide spread of tuberculosis in Chicago, the isolation of patients with the disease in the open, or contagious, stage has come to be considered the important feature in the campaign against this disease. Isolation of patients with tuberculosis in a contagious form from children under 16 years of age was made mandatory in 1917. Despite the energetic and even rigorous enforcement of the law, the number of uncontrolled cases of tuberculosis in the community was not decreased. Hruby [1] stated that in 1931 there were 700 patients on the waiting list of the Municipal Tuberculosis Sanitarium and as many on the waiting lists of the Cook County Hospital and Oak Forest institution. There were 20,000 registered cases in Chicago but only 2,471 available beds. While the idea of isolating patients with open tuberculosis was correct, it failed in its practical application for the simple reason that there was no place for the isolated persons to go.

In 1931 the board of the Municipal Tuberculosis Sanitarium initiated a program of collapse therapy on a mass scale in an attempt to stem the sources of infection. Every suitable patient at the institution and in the field was to receive the benefits of collapse therapy. The results of the campaign have now been analyzed. Of 7,344 patients treated during the period between 1931 and 1936, 3,090 were treated by the induction and maintenance of pneumothorax for more than three months, while 3,584 patients were treated without collapse therapy. Of the 3,090 patients treated, 94.2 per cent had advanced tuberculosis, 84.4 per cent had positive sputum and 81.3 per cent had cavities. Of the total, 14.2 per cent were Negroes. In the collapse group 53.9 per cent were converted from positive sputum to negative, while in the control group the conversion amounted to 15.3 per cent. Thus, since the inception of the program, according to Hruby, 1,285 "fountains of infection" have been shut off. After the treatment 64.3 per cent are still living, as compared with 31.3 per cent in the control group. Of 1,215

1. Hruby, Allan J.: Collapse Therapy of Tuberculosis Seen from the Viewpoint of Control of the Disease in the Community, Am. Rev. Tuberc. **40**: 255 (Sept.) 1939.

patients with positive sputum converted to negative, 227 had been negative from two to three years, 154 for from three to four years, ninety-four for from four to five years, twenty-seven for from five to six years, and twenty-five for six years and over. While the mortality rates for the Municipal Tuberculosis Sanitarium based on a study of 8,779 cases amounted to 82.96 per cent for a five year period and 91.16 per cent for the ten year period, the group in which collapse therapy was practiced showed a survival rate of 69.3 per cent at the end of five years.

Extensive collapse therapy justified itself from the point of view of protecting the community, because it converted a relatively large number of open cases, for which hospitalization facilities did not exist, from a positive to a negative sputum. To overstress the importance of the widest possible collapse program and at the same time to understress or to leave unemphasized the much greater importance of creating facilities for the immediate hospitalization of the tuberculous would be wrong. A more correct orientation toward the pneumothorax therapy would be to regard it as a problem of the individual rather than as a public health measure. Indirectly of course the public would benefit as well. In every urban community there are many persons with unrecognized open tuberculosis. Cases are diagnosed as a rule in the advanced stage of the disease, that is, after countless numbers of others have been exposed to infection. Not all the cases are suitable for collapse therapy and the latter is effective in only a certain proportion. Pneumothorax therapy cannot therefore be regarded as more than a significant aid in the wider problem of the eradication of tuberculosis. The control of this condition is largely a matter of early diagnosis and segregation. No doubt the program would have yielded still better results in Chicago if better facilities for applying the principle of segregation had been available.

## Current Comment

### PRURITUS OF THE ANUS AND VULVA

Medical literature contains a variety of opinions concerning the cause and treatment of pruritus of the anus and vulva. Recently the Haileys[1] stated that the majority of cases of essential, idiopathic or true pruritus of the anus and vulva are due to eczema, the causes of which are essentially the same as those causing eczema in other anatomic localities. The patient's heredity makes a suitable soil for the development of the eczema, as it does for the development of asthma, hay fever, urticaria and migraine in hypersensitive persons. Pruritus of the anus and vulva, in fact, is eczema of those regions and as such is a manifestation of hypersensitiveness in the skin. The direct causes which bring on the attacks may be chemical substances, including some drugs and dyes, clothing, including wool, rubber and some synthetic fabrics, hemorrhoids, diet, heat, atmospheric conditions or perspiration and friction. The Georgia investigators believe that, if it were always possible to obtain a reliable history, almost every case would give a history of hypersensitiveness in the family. In their series of 105 cases, more than 60 per cent gave such a history of manifestations of hypersensitiveness. Benefit in the way of treatment was offered by the roentgen ray. They obtained clinical cures lasting from months to years in 80 per cent of their cases and improvement in an additional 15 per cent. One should insist, however, on having an accurate record of any previous roentgen treatment in order to avoid possible unfortunate sequelae.

1. Hailey, Howard, and Hailey, Hugh: Pruritus Ani et Vulvae, Arch. Dermat. & Syph. **40**: 726 (Nov.) 1939.

### THE ONE HUNDRED AND FIFTIETH ANNIVERSARY OF THE MEDICAL SOCIETY OF SOUTH CAROLINA

At special ceremonies December 5 the Medical Society of South Carolina celebrated its one hundred and fiftieth anniversary. The governor of South Carolina, the mayor of Charleston, the present and retiring presidents of the South Carolina Medical Association, representatives of each county medical society in the state and many others were invited. Dr. Nathan B. Van Etten, New York, President-Elect of the American Medical Association, and Dr. Francis R. Packard, Philadelphia, editor of the *Annals of Medical History*, gave addresses. Dr. James J. Ravenel, president of the Medical Society of South Carolina, gave a historical sketch of the society. Dr. William Weston, Columbia, S. C., presented a tablet from the South Carolina Medical Association, signifying the cordial relation that has existed between the two organizations throughout the history of the state society; especially strong ties between the two organizations have been a mutual interest in medical education and the support of the Medical College of the State of South Carolina. An additional indication of cooperation is the dedication of the current issue of the *Journal of the South Carolina Medical Association* to the Medical Society of South Carolina. This was the only medical organization in South Carolina until 1848, when this society called a convention which formed the South Carolina Medical Association. Although retaining its original name, the older society then became a constituent member of the state association. Dr. James Moultrie was elected president of the new state organization and three years later, when the American Medical Association held its annual meeting in Charleston, he was elected president of the national organization. The Medical Society of South Carolina has taken great interest in promoting public health in its own community. For years it also recorded observations on the weather and conducted a botanic garden as a scientific exhibit; a medical college was established under its auspices more than a hundred years ago. Its members have made many contributions to medicine. It has a collection of books which go back to the day of its birth, including one containing the original minutes of the organization in which new members today still sign their names. The Medical Society of South Carolina is the fourth oldest medical society in the United States, almost as old as the United States government itself.

# ORGANIZATION SECTION

## PROPOSED PROCEDURES OF UNITED STATES CHILDREN'S BUREAU

A meeting of the Committee on Maternal and Child Health of the State and Territorial Health Officers, together with certain representatives of the Children's Bureau advisory committees on maternal and child health, was held at the Children's Bureau, September 9.

The meeting was called to consider problems connected with the increased appropriations for 1940 for maternal and child health as authorized in the amendment to the Social Security Act approved August 10. The meeting had to do with methods rather than policies.

Following are excerpts from a report on the meeting submitted under date of November 14 by the United States Children's Bureau at the request of THE JOURNAL:

A. It is recommended that the additional federal maternal and child health funds should be used (1) to improve quality of services now under way, (2) to extend specific maternal and child health services or (3) to establish demonstrations of types of service needed to enlarge the scope of care and to provide programs of complete maternity care and care of children.

B. It is further recommended that a portion of the additional federal appropriations for fund B be set aside for providing medical, nursing and hospital care for maternity patients and children in selected areas.

C. It is recommended that the use of the new federal funds be limited to one or more of the following types of service:

I. EXPANSION OF ESTABLISHED MATERNAL AND CHILD HEALTH PROGRAMS WITH OPPORTUNITY FOR ADDITIONAL FEATURES

1. Types of Medical Services—

Personnel: (*a*) Full-time pediatricians or obstetricians on state or local staff to assist in administration, conduct or supervision of medical aspects of program.

(*b*) Full-time or part-time pediatricians or obstetricians to provide clinical case consultation or to supervise newly organized outpatient clinics in pediatrics or obstetrics.

(*c*) Qualified local practicing physicians on part-time or fee basis to provide medical care for maternity patients or for infants and children.

(*d*) Other specialists (medical or surgical) as requested by attending pediatrician or obstetrician on part-time or fee basis.

Clinical services: (*a*) Extension of antepartum or child health clinics or conferences.

(*b*) Outpatient clinics in pediatrics or obstetrics, associated with public or nonprofit hospitals, in communities without such clinic services.

(*c*) Hospital or home care for maternity cases or for sick children.

2. Types of Nursing Services—

(*a*) Maternal and child health nursing consultants or supervisors on state or local staffs to assist in administration and supervision of the obstetric and pediatric nursing aspects of the maternal and child health services.

(*b*) Additional qualified public health staff nurses to render generalized public health nursing services which include maternal and child health services, and bedside care of maternity patients and sick children.

(*c*) Bedside nursing service for maternity cases or sick children on case basis by qualified registered nurses under supervision of public health nurses.

3. Other Services—

(*a*) Nutritionists on state or local staff to develop nutrition service in the maternal and child health program.

(*b*) Medical social workers on state staffs in connection with medical care programs for maternity patients or children.

4. Postgraduate Education—

(*a*) In medical centers—clinical courses in pediatrics or obstetrics for general practitioners.

(*b*) Lectures and clinics in communities throughout the states.

(*c*) Postgraduate education and training in pediatrics and obstetrics for full-time medical and nursing or other maternal and child health staff of state or local health agencies.

5. Regulation and Supervision of Maternity Hospitals or Homes.

Recommendations were also made regarding special demonstrations of medical care in maternity or childhood as required by the Social Security Act. These recommendations covered "maternity care and care of newborn infants including program of medical, nursing and hospital care in selected areas, providing payment for care by qualified physicians and nurses at home or in qualified hospitals." Detailed recommendations were made for carrying out these demonstrations. Among these were recommendations that diagnostic and treatment centers were to be organized in suitable hospitals, preference to be given to public hospitals where practicable. A technical advisory committee was recommended in each state to consist of obstetricians and pediatricians, including the chairman of the committee on maternal welfare of the state medical society or other physician designated by the society; the state chairman for the American Academy of Pediatrics and a local practitioner from a small community or rural area, with such other members as the state health department may wish to appoint. All procedures must be according to minimum *Federal Standards* (italics in original), and a detailed descriptive plan for the work must be submitted by the state health department to the Children's Bureau. Extensive requirements for hospitals providing care for maternity patients and newborn infants when such care is paid for from federal maternal and child health funds are outlined. Many of these are already included in the standards of the Council on Medical Education and Hospitals of the American Medical Association and of the American College of Surgeons.

Among other provisions is one to the effect that when maternal or child health care is paid for from federal funds "consultation with specialist in obstetrics" shall be "required prior to any major obstetric operation (mid and high forceps, breech extraction, version, cesarean section, mutilating operations) and for the treatment of serious complications such as eclampsia, placenta praevia, abruptio placentae, unless serious hemorrhage will not permit time to call consultant."

Provisional standards for diagnostic and treatment centers for children in a small city were set up along lines parallel to the maternal care demonstration standards, with preference again given to public hospitals where practicable and with a technical advisory committee of similar composition except that pediatric medical interests instead of obstetric are included.

The agenda for the committee meeting included a discussion of the merit system provided in the Social Security Act, title V, parts 1 and 2 as amended Aug. 10, 1939, which says:

"Clause (3) of Section 503 (a) (and of Section 513 (a)) of such act is amended to read as follows: '(3) provide such methods of administration (including after January 1, 1940, methods relating to the establishment and maintenance of personnel standards on a merit basis, except that the Board shall exercise no authority with respect to the selection, tenure of office, and compensation of any individual employed in accordance with such methods) as are necessary for the proper and efficient operation of the plan.'" [1] Although this merit system was mentioned several times during the meeting there was no genuine discussion of it nor were the details presented to the committee. It is outlined in a circular [2] now issued by the United States Children's Bureau. This circular incorporates the recommendations of the advisory committees briefed in the foregoing and discussions of jurisdiction under the merit system as applied to state employees and local employees; to all intents and purpose it means that any employee in a project carried out with federal funds or with the assistance of federal funds under title V of the Social Security Act will be required to be under the merit system. Exemptions are members of state and local boards or commissions, executive heads of state agencies administering functions provided under title V of the Social Security Act, members of advisory councils, committees or similar bodies paid only for attendance at meetings, and state and local officials serving ex officio or performing incidental duties to such plans. State civil service systems are recognized and cooperation with them is contemplated. There are provisions against discrimination because of an applicant's political or religious opinions. Limitation of political activity is required and classification plan and compensation plans are required.

Permanent employees who have acquired permanent status under a state civil service or merit system established by law do not come under the Social Security Act merit system, but those who have not acquired permanent status but have served satisfactorily may be admitted either to an open competitive examination or to a qualifying examination. Detailed rules are outlined for the recruitment and appointment of new personnel, for registers of eligibles, provisions for making provisional appointments for probationary periods, promotions, furloughs, service ratings and personnel records.

Officers and committee members of state medical societies functioning in cooperation with a state department of health or other state agency operating in conjunction with title V of the Social Security Act should seek for more detailed information relative to these projects from the state board of health. The initiation of state plans is the responsibility of the state health officer. The advisory committees provided include representation of state medical societies in order that the advice of the medical profession in the several states may be available to state health departments through officially constituted channels.

## STATE EDUCATION AND STATE MEDICINE

### A STATEMENT BY THE BUREAU OF MEDICAL ECONOMICS

The state maintains a system of education; why should it not maintain a system of medical care? It protects us against invasion, why not against disease? This is a frequent argument for state medicine. Analogy is proverbially a dangerous foundation for a logical premise. Although most persons are exposed to both disease and education, many persons fail to get either.

In childhood and youth every one needs much the same sort of education. Health and illnesses are as individual as human beings. In adult life there are many who wish to learn the same things, so that books, lectures, classes and the radio can be used effectively for mass treatment of their educational needs. Mass diagnosis and treatment of illness breed disaster! Fairly accurate diagnoses of ignorance and of progress through educational treatment may be made by mass examinations, although even in education there are some doubts as to the accuracy and efficiency of such mass methods.

Ignorance does not appear suddenly or in epidemic form nor does it create an emergency demand for education. The need for education varies only slightly with times and conditions. The positive benefits of education are not confined to the individual. Society realizes a direct return on its investment in the education of its members.

Health and ignorance are alike only in a few features and within those limits the state is already active in both fields. The value of that state activity depends largely on how closely it is limited to the fields for which it is fitted. Whatever can be done for the people as a whole represents activities in which the state may properly concern itself. Where individuals must be distinguished and given widely different and appropriately individualized treatment the mass action of government is seldom successful.

The state can establish quarantine to protect all the people against the invasion of disease; it can collect and tabulate vital statistics pertaining to the whole population; it can assist in health education, urge widespread general immunization and rally the forces to meet the mass attacks of epidemics. Within these and such other limits as have the same qualities and objectives the medical profession has always aided and encouraged state activity.

When individuals are to be aided in the recovery from illness, the analogy of disease with education becomes a contrast. It is seldom that two persons need exactly the same medical care. The nature and

1. Recommended Standards for the Establishment of a Merit System of Personnel Administration and for Qualifications of Certain Classes of Professional Employees in State and Local Agencies Administering Maternal and Child Health Services, Services for Crippled Children, or Child Welfare Services, Under the Social Security Act, Title V, Parts 1, 2 and 3, as amended, Special Information Circular No. 1, U. S. Children's Bureau, Washington, D. C., November 1939.

2. Recommended Standards for the Establishment and Maintenance of a Merit System of Personnel Administration and for Qualifications of Certain Classes of Professional Employees in State and Local Agencies Administering Maternal and Child Health Services, Services for Crippled Children, or Child Welfare Services Under the Social Security Act, Title V, Parts 1, 2 and 3, as amended, Special Information Circular No. 1, U. S. Department of Labor, Children's Bureau, Washington, D. C., Nov. 1, 1939.

degree of illness and the progress of recovery vary widely; moreover, diseases and sick persons cannot be standardized according to the grades as used in the educational system.

Medical service does not fit into time tables or arbitrarily prepared curriculums. It is largely a twenty-four hour service. Its value depends largely on a personal relation between two individuals—the patient and the physician. It must be given at widely varying intervals to each individual who needs and desires the service, and its value depends to a high degree on the way it is suited to each personal requirement.

The reasoning which would have medicine follow the pattern of education is further weakened by an increasing volume of evidence that standardization in education has not been wholly successful. Forcing teachers and pupils into a common mold is held to be destructive of both individual and social values. Such standardization injures those of exceptional ability and thereby deprives the nation of greatly needed intelligent, independent leadership.

The universal and well-nigh equal need for education has not, under governmental control, kept its distribution, both as to quantity and quality, from varying widely in different localities. In spite of the more uniform character of education compared with medical care, few would claim that our educational system is efficiently administered. The thousands of one room schools, of underpaid and poorly trained teachers, and the failure, shown by numerous surveys, of some whole state systems to produce any satisfactory educational results do not encourage application of the same methods to the far more complex problems of personal medical care.

Political influence and pressure groups have worked much harm to education, although it is much better suited to resist or endure such influences than medical service. It is charged that lay supervisors, ignorant of pedagogic methods, hinder professional progress and tend to cripple the freedom of thought and investigation that is of fundamental importance in education. Such influences would be much more destructive in the medical field.

In spite of the fact that education is freely offered by the state to every one and that more than 26,000,000 pupils were in elementary and high schools in 1931-1932, there were at the same time more than 2,700,000 in private and parochial schools. In other words, 10 per cent of the population refused to accept the standardized system for which they had already paid through taxation and preferred to pay a second time for the kind of education they considered more suitable to their individual desires.

The total cost of public day schools amounted to over $2,160,000,000 and the expenditures in universities and colleges was over $600,000,000 more. It was impossible even with these great expenditures and the enormous extent of standardization to provide employment for those who had been accepted as teachers.

In 1936 the Works Progress Administration reported that in January of that year there were 1,218 "physicians, surgeons and dentists" and 40,132 teachers who had been declared eligible for works program employment with the WPA. The effect of the depression was a widespread reduction in educational services and failure to pay those teachers who still remained at their work.

By just so much as education does resemble medical service it seems to have suffered under state administration. Only where the contrast is greatest has it been successful. If a comparison is to be made it would seem to be rather as a warning than as an example.

# OFFICIAL NOTES

## THE NEW YORK SESSION

### Chairman of the Local Committee on Arrangements

Dr. Charles Gordon Heyd, New York, will serve as chairman of the Local Committee on Arrangements for the New York Session, which will be held June 10-14, 1940.

### Applications for Reservations to the Subcommittee on Hotels

The Subcommittee on Hotels of the Local Committee on Arrangements has furnished a list of New York hotels and rates for rooms, which can be found on advertising page 32 of this issue of THE JOURNAL together with an application form that may be used to secure reservations through the Subcommittee on Hotels.

The form printed in the advertising pages may be clipped and, when it has been properly filled in, should be sent at once to Dr. Peter Irving, Chairman of the Subcommittee on Hotels of the Local Committee on Arrangements, Room 1036, 233 Broadway, New York.

If those who expect to attend the annual session of the American Medical Association will send in their applications at the earliest possible time, there should be no difficulty encountered in securing satisfactory accommodations. Applicants for reservations are especially requested to include a second and a third choice in order that good accommodations may be assured if the desired reservation cannot be had at the hotel of preference. It will greatly expedite matters if requests for reservations are addressed directly to Dr. Irving.

## RADIO BROADCASTS

The seventh season of broadcasting by the American Medical Association over the facilities of the National Broadcasting Company and affiliated stations is now under way with programs scheduled each Thursday at 4:30 p. m. eastern standard time (3:30 central standard time, 2:30 mountain time and 1:30 Pacific time). The program is on the Blue network of the National Broadcasting Company, the key station of which is WJZ, New York.

It is impossible to publish a list of topics in advance when programs are developed from last minute proof of pages of THE JOURNAL. It is possible to say that future programs under consideration involve one each dealing with progress in medicine, rabies, infantile paralysis, maternal and child health, hospitals, medical education and industrial health. These programs will be as appropriate as possible to the season at which greatest interest in these topics is manifested. The programs on hospitals, medical education and industrial health will correspond with publication dates of special issues of THE JOURNAL devoted to these topics. The program on medical progress will be broadcast December 28. The programs on maternal and child health will be a part of the spring series.

A special program in cooperation with the National Foundation for Infantile Paralysis, Inc., and the Committee for the Celebration of the President's Birthday is scheduled to appear as the regular program dated January 11.

Lists of radio stations which have signified their intention of broadcasting Medicine in the News, according to information received from the National Broadcasting Company, were published in THE JOURNAL December 2, page 2065.

# Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

## ARIZONA

**Annual Registration Due January 1.**—Every person practicing medicine, surgery or osteopathy in Arizona is required by law to pay annually on or before January 1, to the board of medical examiners, a renewal license fee of $3. Any licentiate who does not renew his license as required above is to be penalized $1 for each day that he practices without a renewal license, not to exceed $50. The board of medical examiners is to revoke the license of any licentiate who fails to renew his license for three successive years.

## ARKANSAS

**Changes in Health Officers.**—Dr. Ulys Jackson, formerly of Marshall, has been assigned as health officer of Boone County with headquarters in Harrison.——Dr. James F. Hays, formerly of Augusta, health officer of Woodruff County, has been placed in charge of the health unit in Pope County with headquarters in Russellville. Dr. Alvie B. Tate, Russellville, health officer in Pope County, will go to Woodruff County.——Dr. Walter W. Brown, Hardy, has been appointed health officer of Sharp County.

**Annual Registration Due January 1.**—Every licentiate of the Arkansas Eclectic Medical Examining Board must register annually with the secretary of the board between January 1 and the last day in February and pay a fee, if a resident of Arkansas, of $2 and, if a nonresident, of $4. The failure of a licentiate to pay the required fee by March 1 automatically suspends his right to practice while delinquent. If he fails for three successive years to pay the required fee, his license is to be canceled, and thereafter he will be reinstated only on such a showing to the board of moral character and professional qualifications as would entitle the applicant to the issuance of an original license and the payment of the same fee as is required for the issuance of an original license.

**Society News.**—At a meeting of the Washington County Medical Society November 7 a symposium on thyrotoxicosis was presented by Drs. Arless A. Blair, Arthur F. Hoge and William R. Brooksher, all of Fort Smith.——The speakers before the Mississippi County Medical Society November 7 were Drs. Henry B. Gotten and Charles G. Andrews, both of Memphis, Tenn., on "Acute Nephritis" and "Salivary Gland Tumors" respectively.——At a meeting of the Benton County Medical Society in Siloam Springs November 9 Drs. George A. Hughes, Siloam Springs, spoke on "Vaginal Hysterectomy" and Harry L. Deutsch, Stilwell, Okla., "Infectious Mononucleosis."——Dr. Pat Murphey, Little Rock, addressed the Pulaski County Medical Society November 20 on "Use of Air in the Treatment of Spastic Paralysis."

## CALIFORNIA

**Annual Registration Due January 1.**—Every practitioner of medicine and surgery holding a license to practice in California is required by law to register annually, on or before January 1, with the secretary-treasurer of the board of medical examiners, and at that time to pay a fee of $2. Failure to pay the required fee within sixty days after January 1 works a revocation of a license, and thereafter a license may be reissued only after application and the payment of a $10 penalty.

**Society News.**—The San Francisco County Medical Society, the Bar Association of San Francisco and the San Francisco District Dental Society held a joint dinner meeting December 7. ——Dr. Vernon P. Thompson, Los Angeles, discussed backache before the San Diego County Medical Society December 12.——At a joint meeting of the staff of Mercy Hospital, San Diego, and the San Diego Academy of Medicine December 6 Dr. A. Graeme Mitchell, Cincinnati, discussed "Medical Caricatures."

**New Building for Research at Stanford.**— A new building for research has been opened at Stanford University School of Medicine, San Francisco, the gift of Mrs. Louis Stern, Palo Alto. Costing about $97,000, the Ruth Lucie Stern Research Laboratory is three stories high, providing more than 6,000 square feet of laboratory space, all of which is exposed to direct outside light. The second floor is occupied by research in pediatrics and the top floor by the gynecologic pathologic section, female endocrine studies and cancer research.

## CONNECTICUT

**Society News.**—The Yale Medical Society was addressed December 13 in New Haven, among others, by Drs. John R. Paul and James D. Trask on "Familial Epidemiology in Poliomyelitis."——Dr. Morris Fishbein, Chicago, Editor of THE JOURNAL, will address the midwinter dinner of the Connecticut State Medical Society January 25 on "American Medicine and the National Government."

**Annual Registration Due During January.**—Every practitioner of medicine and surgery holding a license to practice in Connecticut is required by law to register during January with the state department of health and at that time to pay a fee of $2. Licentiates who have retired from active practice or who live out of the state must register annually but need not pay a fee. A practitioner failing to register is liable to a fine of not more than $5.

## FLORIDA

**Annual Registration Due January 1.**—Every practitioner of medicine and surgery holding a license to practice in Florida is required by law to register annually on or before January 1 with the secretary of the state board of health and at that time to pay a fee of $1. A licentiate failing to register annually is liable to a fine of not more than $50.

**District Meetings.**—At a meeting of the Second District Medical Society in Quincy October 19 the speakers included Drs. Arthur J. Logie, Jacksonville, on "Recent Advances in Tuberculosis"; Frank M. Hewson Jr., Chattahoochee, "Modern Conception of Epilepsy," and Helen W. Bellhouse, Thomasville, Ga., "Undulant Fever in Children: Its Diagnosis and a Report on Two Cases."——The third annual meeting of the South Central Medical District Society was held at Sanford November 2. Among the speakers were Drs. George R. Crisler, Winter Park, on "The Efficacy of Anterior Pituitary Growth Principle in a Diabetic"; Clyde F. Bowie, Leesburg, "Kidney Infection as a Result of Obstruction"; Don D. C. C. Robertson, Orlando, "Inguinal Hernia," and Rollin D. Thompson, Orlando, "A Résumé of the First Year's Work at the State Sanatorium."

## ILLINOIS

**North Central Illinois Medical Meeting.**— The sixty-sixth annual meeting of the North Central Illinois Medical Society was held in Bloomington December 12. The speakers included:

Dr. Benjamin Markowitz, Bloomington, Jaundice Types.
Dr. Emil D. W. Hauser, Chicago, Problems of the Foot.
Dr. Milton G. Bohrod, Peoria, Biopsy of Lymph Nodes for Diagnosis.
Dr. Aaron Arkin, Chicago, Blood Dyscrasias.
Dr. LeRoy H. Sloan, Chicago, Neurologic Problems.
Dr. James Herbert Mitchell, Chicago, Differential Diagnosis of Cutaneous and Mucous Membrane Syphilis.
Dr. Norris J. Heckel, Chicago, Newer Advances in the Treatment of Infections of the Genito-Urinary Tract.
Dr. Edwin M. Miller, Chicago, Fractures About the Elbow.
Dr. Warren H. Cole, Chicago, Surgical Aspects of Diseases of the Pancreas.
Dr. M. Herbert Barker, Chicago, Hypertension.

Drs. Robert S. Berghoff and Donald A. Hirsch, both of Chicago, conducted a heart clinic.

### Chicago

**Personal.**—Dr. Max Thorek, Chicago, was recently made a commander of the Order of St. Alexander of Sofia for his contributions to surgical science. The honor was conferred during the fiftieth anniversary of the founding of the University of Sofia, Bulgaria.

**Millions for Research.**— Northwestern University will receive $1,500,000 and the University of Chicago $1,000,000 under the will of the late Mrs. Clara A. Abbott, widow of Dr. Wallace C. Abbott, founder of the Abbott Laboratories in North Chicago. The money in both instances is to be used for medical, surgical or chemical research. It was announced that the Physiological Building at the University of Chicago would be renamed Abbott Memorial Building, while Northwestern plans to give the name of Abbott Hall to the eighteen story dormitory which is being erected on the Chicago campus. The bequest to the University of Chicago assures an additional grant of $1,500,000 to the university from the

Rockefeller Foundation, which in 1938 offered the grant for research in the biologic sciences on condition that the university obtain an additional $500,000 by 1941.

**Society News.**—The Chicago Society of Internal Medicine was addressed November 27 by Drs. Michael H. Streicher on "Appendicitis—Incidence of Amebiasis in a Clinical Review of 3,407 Cases"; Ralph B. Bettman and Gemma M. Lichtenstein, "Acute Cholecystitis," and Laurence E. Hines, Allen H. Hoover and Edwin Graff, "Effect of Sulfanilamide on the Fibrinolytic Activity of Hemolytic Streptococci."——A symposium on hydronephrosis was presented before the Chicago Council of Medical Women November 8 by Drs. Elizabeth Rothfus Fischer, Elizabeth Clancy, Marie Ortmayer, Lillian Eichelberger and Eleanor M. Humphreys.——The Chicago Ophthalmological Society will be addressed December 18 by Mr. Hugh Hunter, among others, on "Optical Considerations of Contact Lens Prescriptions."——The Chicago Society of Allergy will be addressed December 18 by Dr. Israel Davidsohn on "Pathology of Hyperergic Inflammation."——The speakers before the Chicago Pediatric Society December 19 will be Drs. Philip L. Aries on "An X-Ray Study of the Osseous Development in the Newborn with Special Reference to Congenital Syphilis" and Ernst Gellhorn, "Clinical Implications of Recent Studies on Anoxia and Asphyxia."

## LOUISIANA

**Annual Renewal Due January 1.**—Every practitioner of medicine and surgery holding a certificate to practice in Louisiana is required by law to have his certificate renewed annually on or before January 1 by the secretary-treasurer of the state board of medical examiners and at that time to pay a fee of $2. The board may by unanimous vote revoke any certificate not renewed.

## MASSACHUSETTS

**Society News.**—Among the speakers before the Massachusetts Tuberculosis League November 13 was Dr. Esmond R. Long, Philadelphia, on the uncompliant tuberculosis patient.——Dr. Howard M. Clute, Boston, addressed the Boston Gastroenterological Society November 8 on "Cancer of the Stomach."——At a meeting of the Boston Infectious Disease Society November 2 Drs. William M. Hammon spoke on "Panleukopenia of Cats: A Virus Disease"; William A. Davis, "Observations on the Role of Birds and Mosquitoes in the Spread of Equine Encephalomyelitis," and John R. Mote, "Experiments with Haemophilus Influenzae (Human) in Swine."

**District Meetings.**—At a meeting of the Suffolk District Medical Society in Boston November 29 Drs. William Leifer, Louis Chargin and Harold T. Hyman, New York, discussed "The Theory and Practice of Massive Dose Chemotherapy by the Intravenous Drip Method in the Treatment of Early Syphilis."——The Norfolk District Medical Society devoted its meeting in Boston November 28 to a symposium on the work of certain committees of the state medical societies with the following speakers: Drs. Robert L. DeNormandie, Boston; Michael A. Tighe, Lowell, and Charles C. Lund, Boston.——At a meeting of the Worcester District Medical Society in Grafton November 8 Dr. Charles H. Lawrence, Boston, discussed "Some Practical Uses of Endocrine Therapy" and Dr. Benjamin Cohen, North Grafton, "Comparative Effects of Phenobarbital, Dilantin Sodium and Synergistic Drug Combinations in the Treatment of Epilepsy."——John Howard Mueller, Ph.D., addressed the Middlesex South District Medical Society in Cambridge November 8 on "The Physical and Chemical Properties of Filtrable Viruses."

## MINNESOTA

**The Bell Lecture.**—Dr. Frederick T. Lord, clinical professor of medicine emeritus, Harvard Medical School, Boston, delivered the fifth annual John W. Bell Tuberculosis Lecture before the Hennepin County Medical Society, Minneapolis, December 4. His subject was "The Clinical Aspects and Diagnosis of Pulmonary Lesions."

**Annual Registration Due During January.**—Every practitioner of medicine and surgery holding a license to practice in Minnesota is required by law to register annually during January with the secretary of the board of medical examiners and at that time to pay a fee of $2. A licentiate who practices without renewing his license is guilty of a misdemeanor and is liable to prosecution.

**Rochester's St. Mary's Hospital Observes Anniversary.**—The fiftieth anniversary of the founding of St. Mary's Hospital, Rochester, was celebrated October 27. Among the speakers were Gov. Harold E. Stassen; Dr. Donald Guthrie, Sayre, Pa.; Rev. George Philip Sheridan, D.D., Rochester, "The Hospital and Community Service"; Rev. Alphonse M. Schwitalla, S.J., St. Louis, "Principles of Good Hospital Practice"; Dr. Louis B. Wilson, Rochester, "The Pioneer Sisters," and the Most Rev. John G. Murray, D.D., archbishop of St. Paul, "The Hospital of Tomorrow." The hospital is under the care of the Sisters of Saint Francis of the Congregation of Our Lady of Lourdes. The original building was opened Sept. 30, 1889. Dr. William J. Mayo, assisted by Dr. Charles, performed the first operation, and their father administered the anesthetic. The building was three stories high with a capacity of thirty-three beds. The hospital now has a capacity of 621 beds as compared with 300 at the time it was completely rebuilt in 1922. One feature of the ceremonies held to commemorate the founding of the hospital was the breaking of ground September 30 for a new medical unit, which, when completed, will contain 445 beds and cost more than $1,250,000.

## MISSISSIPPI

**New Building for Health Unit.**—A new building for the Lauderdale County Health Department was recently dedicated in Meridian. Costing more than $50,000, the unit was provided through the cooperation of the Commonwealth Fund of New York, the Mississippi State Board of Health, the city of Meridian and Lauderdale County. It will serve as a public health personnel training center. Dr. Norris C. Knight is director of the county health department.

**Course in Urology.**—The Southeastern branch of the American Urological Association held its sixth annual meeting at Biloxi December 8-9. With its program designed to serve as a postgraduate course for the general practitioner, the speakers included:

Dr. Roy B. Henline, New York, Prostatic Calculi.
Dr. Rubin Flocks, Iowa City, Urinary Calculi.
Dr. Charles M. McKenna, Chicago, The Correction of Some Anomalies of the Genito-Urinary Tract in Children with Special Reference to the Transplantation of the Ureter into the Large Bowel for Bladder Exstrophy.
Dr. E. Granville Crabtree, Boston, Hypertension in Relation to Kidney Disease.
Dr. Edward N. Cook, Rochester, Minn., Urinary Infections.
Col. James E. Ash, Washington, D. C., Bladder Tumors.
Dr. George R. Livermore, Memphis, Tenn., Carbuncle of the Kidney.
Dr. Edgar Burns, New Orleans, Prostatic Obstruction in Negroes.

## NEBRASKA

**Personal.**—Dr. Charles C. Snowden, Davenport, was honored November 9 by a "Pioneer Day" sponsored by the Woman's Club of Davenport. Dr. Snowden has practiced in Davenport fifty-seven years and is still active at the age of 84. A dinner at noon was attended by more than 200 persons and a formal program in the afternoon by about 350. The Rev. A. A. Brooks, Omaha, made the principal address.——Dr. Alva S. Pinto, Omaha, has been appointed health officer of Omaha to succeed Dr. Floyd H. Kinyoun, who resigned.

**Society News.**—Dr. Morris Fishbein, Chicago, Editor of THE JOURNAL, addressed the Omaha-Douglas County Medical Society, Omaha, November 28 on "American Medicine and the National Government."——At a meeting of the Five County Medical Society in Wayne November 6 the speakers were Drs. William R. Hamsa, Omaha, on "Examination and Treatment of Common Back Injuries"; Payson S. Adams, Omaha, "Treatment of Urinary Infections and the Importance of Good Drainage," and Mr. M. C. Smith, Lincoln, executive secretary of the Nebraska State Medical Association, business administration of the association.

## NEW JERSEY

**Society News.**—Dr. Terry M. Townsend, New York, addressed the Essex County Medical Society, Newark, December 14 on "Ballots, Bullets and Bacilli."——Drs. John Russell Twiss and Rupert Franklin Carter, New York, addressed the Bergen County Medical Society, Englewood, November 14 on "Diagnosis and Medical Treatment of Gallbladder Disease" and "Surgical Aspects of Gallbladder Disease" respectively.——Dr. Lester J. Unger, New York, addressed the Atlantic County Medical Society, Atlantic City, November 10 on "Value of Transfused Whole Blood, Citrated Blood and Preserved Blood."

## NEW YORK

**Annual Registration Due January 1.**—Every practitioner of medicine and surgery in New York is required by law to apply annually on or before January 1 to the secretary of the board of medical examiners for a certificate of registration, on application forms furnished by him, and to pay at that time a fee of $2. The law authorizes the secretary of the board to permit secretaries of duly incorporated medical societies to act as his representatives, to receive and transmit to him such applications and fees. Practitioners are liable to severe penalties for failing to register and for continuing in practice thereafter.

### New York City

**Personal.**—Dr. Marion B. Sulzberger gave a series of lectures at the American Institute, November 14, 21 and 28 on "Allergy—A Fundamental Biologic Principle."——Dr. Alexander W. Kruger, deputy medical superintendent of Kings County Hospital, Brooklyn, has been named medical superintendent of Greenpoint Hospital, Brooklyn.

**Third Harvey Lecture.**—Karl F. Meyer, Ph.D., director of the Hooper Foundation for Medical Research and professor of bacteriology, University of California, will deliver the third Harvey Lecture of the current series at the New York Academy of Medicine December 21. His subject will be "The Host-Parasite Relationship with Particular Reference to Heterogeneous Infection Chains."

**"Hibernation" Therapy at City Hospital.**—A special chamber has been installed at City Hospital on Welfare Island to provide facilities for experiments in crymotherapy, popularly known as the "hibernation" or "frozen sleep" method of treating cancer. The room has been made possible by a donation from Mr. and Mrs. Walter C. Baker, New York. The work at City Hospital will be under the direction of a committee consisting of Drs. William Laurence Whittemore, Paul K. Sauer and James R. Lisa. Previous experimental work with this therapy has been carried on at Temple University in Philadelphia.

**Directory of Tuberculosis Clinics.**—The New York Tuberculosis and Health Association has published a new directory of the city's tuberculosis clinics. It lists the chief physician, social worker and supervising nurse affiliated with each clinic and quotes the hours the various clinics are at the public's disposal. The city is served by twenty-five district clinics. Nineteen are operated by the department of health, four by the department of hospitals and two by voluntary hospitals. Sixteen have evening sessions and twenty-three conduct separate sessions for children. Pneumothorax services are available in fourteen. Thirteen consultation clinics are listed, ten operated by the health department and three by the Queensboro Tuberculosis and Health Association. The health department also has a clinic in Lower Harlem conducted as a WPA project for case finding purposes. Copies of the directory may be obtained from the association, 386 Fourth Avenue.

## NORTH CAROLINA

**State Society to Publish Journal.**—The North Carolina Medical Society will begin publication of its own official journal in January with Dr. Wingate M. Johnson, Winston-Salem, as editor. Dr. Thomas W. M. Long, Roanoke Rapids, secretary of the state society, will be the business manager. The journal will be called *North Carolina Medical Journal.*

**Society News.**—Drs. Frank Wilson Jr., Raleigh, and Robert B. Rodman, Wilmington, addressed the New Hanover County Medical Society, Wrightsville Beach, October 19, on "Perforated Peptic Ulcer" and "The Neuroses" respectively.——Dr. Coy C. Carpenter, Wake Forest, addressed the Robeson County Medical Society, Lumberton, in October on diagnosis and treatment of anemia.——Dr. James W. Tankersley, Greensboro, addressed the Guilford County Medical Society, Greensboro, recently on "Splenomegaly, Its Physiology, Pathology and Treatment."——Drs. Hillis L. Seay, Huntersville, and Thomas C. Bost, Charlotte, addressed the Mecklenburg County Medical Society, Charlotte, October 17 on treatment of tuberculosis and the technic of treating hernia, respectively.——A symposium on sulfanilamide and sulfapyridine was presented before the Buncombe County Medical Society, Asheville, November 6 by Drs. John C. Young, Wilson Pendleton and John LaBruce Ward. A symposium on the common cold from the point of view of the nose and throat physician was presented by Drs. Lewie M. Griffith, Cecil L. Crump and Cecil C. Swann November 20. All are of Asheville.

## NORTH DAKOTA

**Annual Registration Due January 1.**—Every practitioner of medicine and surgery holding a license to practice in North Dakota is required by law to register annually on or before January 1 with the secretary-treasurer of the board of medical examiners and at that time to pay a fee of $5 if a resident of North Dakota or $2 if a nonresident. A practitioner may not lawfully practice if he has not registered. If he does so his license may be revoked and can be reinstated on the payment of unpaid fees and $0.50 each month of default.

## OHIO

**Personal.**—Dr. Carlos Eugene Pitkin, assistant clinical professor of otolaryngology at Western Reserve University School of Medicine, Cleveland, has been promoted to clinical professor, succeeding the late Dr. William B. Chamberlin. Dr. Pitkin has been a member of the faculty for twenty-three years.

**Toledo Clinic Day.**—Dr. Francis D. Murphy, Milwaukee, was the guest speaker at the annual clinic day sponsored by the Academy of Medicine of Toledo and Lucas County November 17. Dr. Murphy spoke in the afternoon on "Some Phases of Jaundice and Its Significance" and "Hypertension and Nephritis." The morning was devoted to clinics at Mercy Hospital.

**Society News.**—Dr. William H. Weir, Cleveland, discussed "Conservatism in Certain Gynecologic Conditions" at the meeting of the Academy of Medicine of Cincinnati November 28 under the auspices of the Cincinnati Obstetrical Society.——Dr. Herman W. J. Koerper, Columbus, addressed the Stark County Medical Society, Canton, November 15 on "Toxemia of Pregnancy."——Dr. Frederic Schreiber, Detroit, addressed the Summit County Medical Society, Akron, December 9 on "Cerebral Anoxia and Anesthesia."——Dr. Tom Douglas Spies, Cincinnati, addressed the Academy of Medicine of Cleveland December 15 on "The Vitamin B Deficiencies."

## PENNSYLVANIA

**Annual Registration Due January 1.**—Every practitioner of medicine and surgery holding a license to practice in Pennsylvania is required by law to register annually on or before January 1 with the board of medical education and licensure in the department of public instruction and to pay a fee of $1 or such fee as may be fixed by the department of public instruction. A practitioner who fails to register and who continues to practice is liable to a fine of from $10 to $100.

**Society News.**—Dr. Roland S. Aronson, Philadelphia, addressed the Northampton County Medical Society, Easton, November 17 on the cancer control program in Pennsylvania.——Drs. John Eiman, Abington, and Damon B. Pfeiffer, Philadelphia, addressed the Cambria County Medical Society, Johnstown, November 9 on "Broader Aspects of Arterial Diseases with Special Reference to Etiology" and "Carcinoma of Rectum and Rectosigmoid" respectively.——A symposium on pneumonia was presented before the Westmoreland County Medical Society at the Mountain View Hotel near Greensburg November 21 by Drs. Bernard J. McCloskey, Johnstown; Carl E. Ervin, Harrisburg, and James W. Strang, Pittsburgh.

### Philadelphia

**National Defense on the Program.**—The Philadelphia County Medical Society held its second annual "National Defense Night" November 27. The speakers were:

Lieut. Col. John F. Corby, Philadelphia, The Newer Army Medical Service.
Lieut. Col. William D. Fleming, Edgewood Arsenal, Md., Medical Aspects of Chemical Warfare.
Dr. Robert Olesen, U. S. Public Health Service, New York, Quarantine Too Is Streamlined.
Lieut. Comdr. Herbert L. Pugh, Naval Hospital, Philadelphia, Activities of the Naval Medical Corps in Guam.

A film prepared by the War Department, "Chemical Warfare Company in Combat," was shown.

### Pittsburgh

**Society News.**—Dr. William James Gardner, Cleveland, will address the Allegheny County Medical Society December 19, on "Development of Modern Surgery of Brain." Other speakers will be Drs. John Day Garvin on "When Does a Duodenal Ulcer Become Surgical?"; Thomas C. Wilkinson, "Treatment of Tetany with Dihydrotachysterol," and Gregg A. Dillinger, "A True Evaluation of Tonsillectomy by Electrocoagulation."

## SOUTH CAROLINA

**Personal.**—Dr. James C. Brabham, formerly of Johnsonville, has been made health officer of Colleton County with headquarters at Walterboro, succeeding Dr. Clarence L. Guyton, who has been placed in charge of cancer control work of the state department of health.——Dr. Charles M. Moore, St. George, former health officer of Dorchester County, has been appointed director of the new mobile syphilis clinic in Charleston County.

**Society News.**—Dr. Nathan B. Van Etten, New York, President-Elect of the American Medical Association, addressed the Columbia Medical Society recently on "The Quality of Medicine." Dr. James E. Boone, Columbia, presented a paper on "Prophylaxis of Recurrent Renal Calculi." Dr. Allen F. Voshell, Baltimore, addressed the society recently on "Oft Forgotten Facts About Fractures," and Dr. James R. Allison, Columbia, on "Twenty Years' Experience in the Treatment of Skin Cancer."——Dr. Emory Hill, Richmond, Va., was the guest speaker at the annual meeting of the South Carolina Society of Ophthalmology and Otolaryngology in Columbia November 7. His subject was "Some Problems of Cataract Surgery."

## SOUTH DAKOTA

**Health Officers Elect.**—Dr. Henry Russell Brown, Watertown, was elected president of the South Dakota Health Officers Association at its annual meeting in October. Dr. Robert S. Westaby, Madison, was made vice president and Dr. John F. D. Cook, Pierre, reelected secretary.

## TENNESSEE

**Society News.**—Dr. William H. Sebrell Jr., Washington, D. C., of the U. S. Public Health Service addressed the Sullivan-Johnson Counties Medical Society, Bristol, November 1 on diseases of nutritional deficiency with special emphasis on pellagra.——Drs. Ernest Marcus and Charles K. Slade, Mountain Home, among others, addressed the Washington County Medical Society, Johnson City, November 2 on "Some Untoward Reactions in Arsphenamine Therapy" and "Serial Pyelography" respectively.——Dr. Barney Brooks, Nashville, addressed the Nashville Academy of Medicine and Davidson County Medical Society, Nashville, December 5 on surgery of the thyroid gland.——Speakers before the Dyer, Lake and Crockett Counties Medical Society November 1 were Drs. Frank D. Linn, Memphis, on "Mastoid Disease"; Clyde V. Croswell, Memphis, "Administration of Fluids," and Robert L. Sanders, Memphis, "Peptic Ulcer: Diagnosis and Management."——Drs. Gilbert M. Roberts and Edward F. Buchner Jr. addressed the Chattanooga and Hamilton County Medical Society November 23 on "Chronic Nonpurulent Urethritis in Women" and "Ten Year Study of Local Maternal Mortality" respectively.

## TEXAS

**Annual Registration Due January 1.**—Every practitioner of medicine and surgery holding a license to practice in Texas is required by law to register annually on or before January 1 with the state board of medical examiners and at that time to pay a fee of $2. If a practitioner fails to renew his registration within sixty days after January 1 his license is suspended.

**Tri-State Meeting.**—The thirty-fourth annual meeting of the Tri-State Medical Society of Louisiana, Arkansas and Texas was held in Marshall November 8-9 under the presidency of Dr. Joseph D. Roberts Jr., Longview. Among the speakers were:

Dr. Guy A. Caldwell, New Orleans, Foot and Leg Deformities in Infants and Young Children Associated with Overweight.
Dr. Millard F. Arbuckle, St. Louis, Bronchoscopy as an Aid in the Diagnosis and Treatment of Diseases of the Pulmonary Tract.
Dr. Calvin R. Hannah, Dallas, Toxemia of Pregnancy.
Dr. George B. Fletcher, Hot Springs National Park, Ark., Underwater or Pool Treatment of Certain Abnormal Conditions of Muscles, Nerves and Joints.
Dr. Charles T. Stone, Galveston, Vitamin K and Its Clinical Applications.

## WEST VIRGINIA

**Public Health Meeting.**—Dr. William H. Riheldaffer, Romney, was elected president of the West Virginia Public Health Association at its annual meeting in Fairmont November 6-8. Among speakers at the meeting were Drs. Karl A. Menninger, Topeka, Kan., on "Should a Democracy Be Concerned with the Mental Health of Its Citizens?"; Joseph W. Mountin, U. S. Public Health Service, "What Should a Public Health Program Include?" and Halbert L. Dunn, chief of vital statistics division, U. S. Bureau of the Census, Washington, "Democracy in the Everyday Administration of Public Health."

## GENERAL

**Prize for Research in Ophthalmology.**—The trustees of the Association for Research in Ophthalmology announce that a cash prize of $100 will be awarded at the 1940 meeting for the paper which in their judgment shows most originality and exemplifies best the spirit of research in ophthalmology. Dr. Cecil S. O'Brien, University Hospitals, Iowa City, is secretary of the association.

**Hygiene Association Disapproves Sex Lecturer.**—The American Social Hygiene Association requests publication of a statement that the use of the association's name in certain sex publications by one Mrs. Jardine McCree is unauthorized and heartily disapproved. The association has received reports from various parts of the country that Mrs. McCree is giving lectures and showing films on sex that are objectionable. In a booklet sold in connection with the lectures entitled "Sex Problems and Advice" the name and address of the American Social Hygiene Association is printed, giving the impression that the woman is in some way connected with the organization.

**Warning Against Impostor.**—An Iowa physician sends a warning against one William J. Collins, who represents himself as a physician and a war veteran. Collins recently telegraphed to an Iowa town for a physician to meet the train on which he was arriving. He then decided to stop there. He appeared to be suffering from carcinoma of the bladder with profuse hemorrhage, and was also a morphine addict. He had medical and nursing care at a hotel and asked to have bills sent to the Veterans Administration. The facility at Hines, Ill., to which the bill was sent, reported that Collins had several times incurred expenses without authority and requested to have the bills sent to that hospital. No record of his case exists there, it was stated. In addition to his expenses he borrowed $36.20 from the physician who attended him, giving a bad check therefor. Collins said he lived at Lake Worth, Texas. The American Medical Association, however, has no record of a physician of that name licensed to practice in Lake Worth.

**Special Society Elections.**—Dr. Charles A. Doan, Columbus, was elected president of the Central Society for Clinical Research at its twelfth annual session in Chicago November 3-4, succeeding Dr. Walter H. Nadler, Chicago. Dr. Lawrence D. Thompson, St. Louis, secretary-treasurer of the society, was made vice president and Dr. Carl V. Moore, St. Louis, secretary-treasurer. The 1940 session will be held in Chicago November 1-2.——Dr. Harry R. Foerster, Milwaukee, was elected president of the American Academy of Dermatology and Syphilology at its annual meeting in Philadelphia November 6-8. Dr. Clark W. Finnerud, Chicago, was made vice president and Dr. Earl D. Osborne, Buffalo, reelected secretary. Next year's meeting will be in Chicago.——Dr. Thomas T. Mackie, New York, was named president-elect of the American Society of Tropical Medicine at the annual meeting in Memphis, Tenn., November 21-24; Malcolm H. Soule, LL.D., Ann Arbor, Mich., vice president, and Dr. E. Harold Hinman, Wilson Dam, Ala., secretary. Dr. Louis L. Williams Jr., Washington, D. C., became president.

**Changes in Status of Licensure.**—The Illinois Department of Registration and Education announces the following:

Dr. William W. White, Chicago, license restored October 6.

The Michigan State Department of Registration in Medicine announces the following:

Dr. Charles L. Soper, Barryton, Mich., license revoked recently for unprofessional conduct.

The Pennsylvania State Board of Medical Education and Licensure has reported the following action:

Dr. Henry L. Westermann, Pittsburgh, license revoked recently because of his breaking parole after conviction in federal courts.

The Texas State Board of Medical Examiners recently reported:

John G. Townsen, Lampasas, Texas, license reinstated July 30; it was revoked in 1934.

The State of Utah Department of Registration recently reported the following action:

Dr. Afton M. Livingston, whose last known address was Manti, Utah, license restored August 1.

**Society News.**—The American Social Hygiene Association announces the fourth annual Social Hygiene Day to be observed Feb. 1, 1940. Plans indicate that there will be more than 5,000 community and regional meetings over the country. Among features of the observance will be the release of a new sound motion picture entitled "With These Weapons." Those desiring information concerning participation in the observance are asked to write to Social Hygiene Day Service, American Social Hygiene Association, 50 West Fiftieth Street, New York.——The United States Chapter of the International

College of Surgeons will hold its fourth annual assembly at Venice, Fla., Feb. 11-14, 1940. There is no registration fee. For general information address Dr. Fred H. Albee, 57 West Fifty-Seventh Street, New York; for information about presentation of papers or exhibits write to Dr. Charles H. Arnold, secretary of the scientific assembly, Terminal Building, Lincoln, Neb. —— Dr. Amos L. Beaghler, Denver, was elected president of the American School Health Association at the annual meeting in Pittsburgh in October. —— The American Student Health Association will hold its annual meeting at the Hotel New Yorker, New York, December 28-29. —— New officers of the Central Neuropsychiatric Association are Drs. Percival Bailey, president, Chicago; Francis A. Ely, Des Moines, vice president, and William C. Menninger, Topeka, Kan., secretary-treasurer. The 1940 session will be held in October in Milwaukee. —— The Phi Lambda Kappa Medical Fraternity will hold its thirty-second annual convention in New York December 30-January 1 at the Park Central Hotel.

**Eighth American Scientific Congress.**—The Department of State announces that the Eighth American Scientific Congress will be held in Washington, D. C., May 10-18, 1940, under the auspices of the government of the United States. The meeting will be one phase of a celebration of the fiftieth anniversary of the founding of the Pan American Union. The congress will be divided into the following sections: anthropologic sciences, biologic sciences, geologic sciences, agriculture and conservation, public health and medicine, statistics, history and geography, international law, public law and jurisprudence, economics and sociology, education. The official languages will be English, Spanish, Portuguese and French. Papers may be presented in any of these languages and arrangements will be made for presentation of the papers or résumés thereof in the other languages. Secretary of State Cordell Hull has appointed the following organizing committee to cooperate with the Department of State in formulating plans:

The Honorable Summer Welles, under secretary of state, chairman.
Warren Kelchner, acting chief, division of international conferences, Department of State, vice chairman.
Alexander Wetmore, Sc.D., assistant secretary, Smithsonian Institution, secretary and secretary general of the congress.
Charles G. Abbot, LL.D., secretary of the Smithsonian Institution.
Isaiah Bowman, LL.D., president, Johns Hopkins University, Baltimore.
Vannevar Bush, D.E., president, Carnegie Institution of Washington.
Ben M. Cherrington, Ph.D., chief, division of cultural relations, Department of State.
Mr. Laurence Duggan, chief, division of the American republics, Department of State.
Dr. Ross G. Harrison, New Haven, Conn., chairman, National Research Council.
Waldo G. Leland, secretary, American Council of Learned Societies.
Mr. Archibald MacLeish, librarian of Congress.
Dr. Thomas Parran, surgeon general, U. S. Public Health Service.
Stuart A. Rice, Ph.D., chairman of the Central Statistical Board.
Leo S. Rowe, LL.D., director general, Pan American Union.
James Brown Scott, J.U.D., trustee and secretary, Carnegie Endowment for International Peace.

This congress is an outgrowth of the First Latin American Scientific Congress held in Buenos Aires in 1898. The second was in Montevideo in 1901 and the third in Rio de Janeiro in 1905. In 1908 the United States was invited to participate and the name was changed to the First Pan American Scientific Congress. Subsequent meetings were held under this name in Washington in 1915, Lima, Peru, in 1924 and Mexico City in 1935. The latter session, in recognition of the continuity of the preceding congresses, was called the Seventh American Scientific Congress.

## FOREIGN

**Kitasato Institute Twenty-Five Years Old.**—The Kitasato Institute for Infectious Diseases celebrated its twenty-fifth anniversary November 5. The institute was founded by Baron Kitasato, the Japanese bacteriologist who discovered the bubonic plague bacillus, after he had served many years as director of the Imperial Japanese Institute for the Study of Infectious Diseases. Baron Kitasato was born in 1856 and died in 1931.

**Ear, Nose and Throat Congress Postponed.**—The committee of the Fourth International Oto-Rhino-Laryngological Congress, which was to have been held in 1940 in Amsterdam, has been postponed indefinitely. Dr. A. Marres, Willemsparkweg 31, Amsterdam, is secretary of the congress. The committee expresses the hope that "the present horror will give way to better times and that at some future date it may be granted to us to send our invitation once more to the otorhinolaryngological world."

**New Medical Center in Sweden.**—The Carolinian Hospital, part of a new medical center in Stockholm, Sweden, is nearing completion, according to a recent announcement. The hospital will provide accommodations for about 1,500 patients and more than 1,000 doctors, nurses and other personnel. On the roof of the main buildings there will be a sun terrace 650 feet long. A mural painting on the ceiling of the vestibule by Prince Eugen of the royal family represents the aims of medical science. Provision is being made to protect the hospital from air raids. Subterranean rooms are being blasted in the rock under the hospital to make shelters and an emergency hospital. The medical center, which includes numerous buildings for research, isolation, administration, training, housing and a college of nursing, will provide training and study facilities for the students of the Carolinian Medico-Surgical Institute, which is gradually moving into the new premises. Among buildings already opened are a home for the crippled and the "Radium Home," a cancer hospital. The eventual cost of the center will be about $10,000,000, of which about two thirds has been expended.

### Deaths in Other Countries

**Edward Palmer Poulton,** senior physician to Guy's Hospital, London, England, died October 18 at Tunbridge Wells, aged 56. Dr. Poulton was well known for his work on several editions of Taylor's Practice of Medicine.——**Prof. Dr. Freiherr v. Eiselsberg,** head of the First Surgical University Clinic at Vienna, aged 79, died October 26 of skull fracture resulting from a railroad accident en route from his estate near Wels to Vienna. Professor Eiselsberg and Dr. Julius Wagner-Jauregg were the only two remaining in good health who had seen the brightest period of the Medical Faculty of Vienna. ——**Dr. Wilfred Trotter,** sergeant surgeon to the king of England since 1932 and professor of surgery at the University College Hospital Medical School, died November 25 at Blackmoor, Hampshire, England, aged 67.

# *Government Services*

### Dr. Griffitts Goes to Puerto Rico

Dr. Thomas H. D. Griffitts, senior surgeon of the U. S. Public Health Service and director of the Henry R. Carter Memorial Laboratory, Savannah, Ga., has been transferred to Puerto Rico and the Virgin Islands, it is reported. He will be succeeded at the laboratory by Dr. Charles M. McGill, assistant surgeon, U. S. Public Health Service. Dr. Griffitts has been in Savannah since 1937, when the memorial laboratory was opened.

### New Members of Advisory Cancer Council

Drs. Max Cutler, director of the Chicago Tumor Institute, and George M. Smith, research associate in anatomy, Yale University School of Medicine, New Haven, Conn., have been appointed members of the National Advisory Cancer Council to succeed Dr. Ludvig Hektoen, Washington, D. C., and Clarence C. Little, Sc.D., Bar Harbor, Maine, whose terms have expired. The Council held its first quarterly meeting in the new National Cancer Institute near Bethesda, Md., December 4. Continuing members are James B. Conant, Ph.D., president of Harvard University, Cambridge, Mass.; Arthur H. Compton, Ph.D., Chicago; Drs. Mont R. Reid, Cincinnati, and James B. Murphy, New York.

### Positions Open at St. Elizabeths

The United States Civil Service Commission announces open competitive examinations for two positions as junior medical officer at St. Elizabeths Hospital, Washington, D. C., one a rotating internship and the other a psychiatric residency. Both carry salaries of $2,000 a year. The internship consists of a rotating service of four months of surgery, four months of acute medical service, four months of chronic medical service, two months of obstetrics, two months of pediatrics, three months of general laboratory work and six months of psychiatry. The residency is a postgraduate internship of one year, offered to graduates in medicine who have already served an accredited internship. Application forms may be obtained from the secretary of the board of civil service examiners at any first class post office, from the commission at Washington or from the district office in any of the following cities: Atlanta, Boston, Chicago, Cincinnati, Denver, New Orleans, New York, Philadelphia, Seattle, St. Louis, St. Paul, San Francisco, Honolulu, Balboa Heights, C. Z., and San Juan, P. R.

# Foreign Letters

## LONDON

*(From Our Regular Correspondent)*

Nov. 11, 1939.

### The Chemotherapy of Infected War Wounds

The war office has distributed to all officers of the Royal Army Medical Corps a memorandum on the treatment of infected war wounds by the sulfonamide derivatives which may be taken as reflecting the authoritative British view on these substances. As they have been shown to be effective in streptococcic infections and also to have an action on anaerobic gas forming bacilli, it is recommended that they be given a trial in the field. The earlier the treatment the better the result, but some benefit may be anticipated even in established infections. All wounds which appear likely to become the site of secondary coccic or gas gangrene infection should receive as soon as possible a prophylactic course of sulfonamide treatment, which should occupy about forty-eight hours. For developing or established infections the course should extend over ten days, but if not then effective an interval of forty-eight hours should be allowed before continuing treatment. When an infection appears to be controlled, as judged by the temperature, small doses should be continued for a further three to five days in order to prevent relapses. The principle of effective treatment is to obtain a high blood concentration of the drug as soon as possible and to maintain this at an effective level for a time. As the drugs are rapidly excreted, to maintain an effective level it is necessary to administer them at four hour intervals day and night.

The dose of sulfanilamide recommended for prophylaxis is 4 Gm. at once followed by 2 Gm. after four hours and then by 1 Gm. every four hours day and night. If, after ten days, infection is still uncontrolled, allow an interval of forty-eight hours and then repeat the same course from the beginning or, if available, change to sulfapyridine. If infection appears to be controlled during the first or later courses, reduce the dose to 0.5 Gm. and continue for three to five days after the temperature has become normal. If during the first course of treatment no effect is evident in three days, a change to sulfapyridine is recommended.

For sulfapyridine treatment powdered tablets should be administered in milk or water. If vomiting is troublesome the dose should be split and administered at shorter intervals. For prophylaxis 3 Gm. should be given at once followed by 2 Gm. in four hours and then by 1 Gm. every four hours day and night for forty-eight hours. Soluble sulfapyridine is of great value when swallowing is impossible or gastric trouble prevents absorption. It may be injected intramuscularly or intravenously in doses of 1 Gm. every four hours day and night. The prophylactic course is completed in forty-eight hours. For treatment the course may be continued for ten days, but a change should be made to the oral compound as soon as possible. The soluble compound finds its best use in the initial phases of a course of treatment and should not be regarded as a substitute for the oral compound. It should be used for a continuous course only when oral therapy is impracticable.

### Traffic Accidents Increased by the Blackout

The danger of air raids prevents street lighting and compels the screening of traffic lights and the confining of illumination to interiors. The result at night is a condition of darkness for which the term blackout is used. The result is a great increase in traffic accidents. In October 919 persons were killed in these accidents, against 641 in October 1938 and 1,130 last September, the first month of the blackout. The returns show for the first time the number of fatalities during the hours of darkness. Of 572 pedestrians killed in October, 424 were killed in the darkness; the total number of persons killed was 564. In London the fatalities in October numbered 131, of which eighty-four occurred in the darkness. If the number of deaths in road accidents in the blackout continues at the present rate, in a three years war it will total nearly 40,000. At a press conference arranged by the "National Safety First Association," it was stated that an analysis shows that about one third of those killed in traffic accidents since the war started were over 70 years of age, one third between 60 and 70, one sixth between 50 and 60, and one sixth under 50. If elderly people refrained from going out during the blackout except when absolutely necessary, accidents would be greatly reduced. It has been found that a large percentage of the accidents are caused by pedestrians stepping into the path of a car in the belief that the driver would see them. The pedestrian has not been able to get rid of his peace time road psychology and thinks he will be seen.

### Special Types of Injuries in Air Raids

The extent of the arrangements for the treatment of injuries to civilians in air raids is shown by the provision by the government of special centers where certain types of disability can be collected and treated by specialist staffs. But it is recognized that in the early stages of an emergency it is likely to prove impracticable to divert systematically these cases to such special centers, owing to difficulties in switching suddenly over from a central peace time to a decentralized war time organization, and to the impossibility of foreseeing the conditions in which it will be necessary to work in the first instance. Nevertheless the locality of the special centers is being prearranged and they will function at the earliest possible moment. In the case of neuroses uncomplicated by any injury, an endeavor will be made from the outset to dispose of those requiring special treatment, that is, unfit to be sent home, by sending them to the special institutions to be established. Plans are being made for collecting from the central hospitals such special equipment as is necessary. Specialist staffs also are being selected.

### The Illicit Drug Traffic

In spite of the efforts of the League of Nations to check the illicit drug traffic, it still continues on a large scale. In the House of Commons a member pointed out that, while good work toward its suppression has been shown by most governments, the Japanese fostered the consumption of drugs not only in China but all over the world, including Canada, and they smuggled cocaine into India.

Mr. Butler, undersecretary for foreign affairs, said that the government viewed with grave concern the drug situation described by the Opium Advisory Committee last June and reviewed by the League of Nations this autumn. A serious feature was the growth of the use of heroin, the effects of which were far more serious than those of opium. In 1936 there was an Anglo-Japanese drug traffic agreement. No immediate action followed till they arranged this autumn for closer cooperation with the Japanese government. The information in his possession did not show that the increase of the drug traffic in China was the outcome of any deliberate plan of the Japanese government. In North China, the central government attempted to enforce drastic opium and narcotic laws, but since the Japanese occupation these deterrents had disappeared. In central China the position did not seem so serious. The British government intended to continue its efforts in cooperation with other governments.

### Closure of the Ductus Arteriosus—A Correction

In the London letter in THE JOURNAL June 24, page 2617, reference was made to the paper by Barclay, Barcroft, Barron and Franklin in the *British Journal of Radiology* reporting identification of the ductus arteriosus in the newborn lamb. The same authors in the September issue of the *British Journal*

*of Radiology* report that, since that time, owing to improvements in technic, they have found that their report was erroneous. The shadow which was then described as that of the ductus is really that of a branch of one of the pulmonary arteries.

## BERLIN

*(From Our Regular Correspondent)*

Nov. 8, 1939.

### Race and Heredity

Since the report on heredity and race in THE JOURNAL July 29, page 434, additional information has become available. It has been decided to avoid using the term "Aryan" in official publications. Dr. Gross, director of the state bureau of race and politics, explained this to an assembly of leaders of the Hitler Youth movement. It is difficult, he said, to define the term "Aryan" because the expression is derived from philology and does not always coincide with present racial knowledge. For that reason the terms cross breeds (mischlinge) of the first and second grade have been adopted. This corresponds to terminology used in cattle raising. (See THE JOURNAL, Sept. 8, 1934, p. 764, for criticisms of the use of "Aryan" in the sense given it in Germany.)

A race museum is to be founded in Berlin to serve primarily the idea of race significance as a universal political concept. Attention is called to the remarks made by an official representative at the second university week at Karlsruhe: "Efforts to measure race craniologically are likely to introduce explosive matter into the unity of the German people." Heretofore cranial measurements as factors in race determination have been popular. A Jewish physician in Hamburg, 52 years old, was sentenced in July of this year to fifteen years in the penitentiary and ten years of civic degradation because of being involved in five cases of race pollution; that is, intercourse with Aryan women. To promote the study of heredity, local health bureaus have been ordered to keep official records of multiple births; that is, of twins, triplets and so on, as well as records of consanguineous marriages. Statistics of this kind are regarded as valuable for the biology of heredity.

Hereditary diseases are also exploited with official approval on the stage. A strolling theatrical company is presenting a play which in itself is of no significance and perhaps would never have been written or shown without government support. The play hinges on the idea that epilepsy was discovered in the bridegroom. The betrothal is annulled and the man sterilized. This play was presented also during a "district cultural week."

The danger of asocial persons to the welfare of the nation has been made the object of extensive investigations by the same bureau on race and politics in Bremen and Saxony. It is alleged that the evaluation of the facts already secured makes possible proof that asocial persons constitute a biologic danger. The first publication of the results of investigation concern three asocial families. Dr. Knorr, of the same bureau, regards asocial persons as an inferior biologic stock and the task of reducing the progeny in such families as the most important problem in the purification of heredity stocks. While the size of the average German family is insufficient to prevent a decline in population, the number of children in asocial families is several times as large. The investigations conducted did not deal with criminals and gypsies but with asocials who stand out not because of individual criminal acts but because of their general incapacity for social cooperation. On the basis of these investigations, Knorr contradicts the customary view that asocials are found in families otherwise useful and that their descendants ought to be preserved. The investigations, he says, show that nearly all members of investigated families and their kin are incapable of social cooperation. These asocial characteristics have been transmitted by heredity. The offspring of such marriages is unusually high. The menace represented by asocials is not of a medical nature but one of character. A law making it possible to sterilize such descendants who have early manifested asociality would essentially reduce this inferior social stock within a few generations. It was stressed that asocial persons may not be placed in the same category with persons hereditarily diseased in the legal sense of the word.

## COPENHAGEN

*(From a Special Correspondent)*

Nov. 21, 1939.

### The Serum Treatment of Poliomyelitis

The waves of poliomyelitis which have swept over Denmark almost every late summer and autumn in recent years should have given opportunities, one would have thought, for testing the efficacy of the serum of convalescents. In the outbreak of 1934, for example, serum was administered in about 80 per cent of all the well defined cases, and Dr. Claus Jensen, who undertook a statistical study of this year's cases, formed a favorable opinion of this treatment. Yet faith in it has languished ever since, many clinicians, as distinct from statisticians, having been disillusioned in this matter. So when in 1937 a new outbreak occurred, the Blegdam Fever Hospital serving Copenhagen dispensed with this treatment. It was only in the provinces in 1937 that a lingering belief in the efficacy of serum secured its employment in a limited number of cases.

In 1939 Dr. E. Juel-Henningsen and Dr. G. Rasch issued a study of this problem with reference to the outbreak of poliomyelitis in 1937. They sent a questionnaire to the hospitals, which had dealt with more than a thousand cases that year, and analyzed the answers. In the provinces there were 489 patients receiving serum treatment and 400 who received no serum. While 60 per cent of the latter developed paralysis, only 33 per cent of the recipients of serum did so. Another comparison, much less favorable to serum, was made between 409 serum-treated patients who were not paralytic on admission to the hospital and 200 patients who were not given serum and who were also not paralytic on admission. Subsequently 18.1 per cent of the serum-treated group and 19 per cent of the controls developed paralysis. The scoffing clinician must feel tempted by such results to suspect the statistician of being capable of coming to any result he likes by an adroit reshuffling of the cards. At all events in Denmark at present there is a conviction that the wholesale early treatment of poliomyelitis with the serum of convalescents still lacks convincing proofs of its efficacy.

### The Pirquet or the Mantoux Test?

The Norwegians usually employ the Pirquet test, while the Danes prefer the Mantoux test, which they consider much more delicate and accurate. The Norwegians have found that two consecutive Pirquet tests on Mantoux-positive persons give positive reactions in from 90 to 95 per cent. This they consider good enough and they continue to prefer the Pirquet test for wholesale examinations of children, holding that its comparative simplicity compensates for the small margin of error inherent in it. The Danes, however, have found that only from 50 to 70 per cent of their Mantoux-positive reactors also give a positive reaction to the Pirquet test; hence the disfavor into which it has fallen in Denmark. Swedish observers are, on the whole, inclined to side with the Danes in this matter, though tuberculin testing in Sweden has not brought such general discredit on the Pirquet test as it has in Denmark.

To clear up this minor dispute, Dr. T. Madsen, of the State Serum Institute in Copenhagen, and Dr. O. Scheel, of the Ullevaal municipal hospital in Oslo, arranged a combined Norwegian-Danish investigation. Dr. J. Holm represented Denmark and Dr. H. J. Ustvedt represented Norway. They worked together in Copenhagen, testing 258 school children

and seventy-two young adults. When the Pirquet test was repeated twice, it gave a positive reaction in 90 per cent of the Mantoux-positive children and in 87 per cent of the Mantoux-positive young adults. These investigators suggest that reinfections maintain sensitiveness to tuberculin and that the more a community is rid of tuberculosis the greater will be the proportion of Pirquet-negative persons among the Mantoux positive. And Norway, with its comparatively high tuberculosis morbidity, must therefore provide a greater proportion of Pirquet-positive reactors than Denmark.

### Gonorrhea and Modern Chemotherapy

In a report recently presented to the Danish Medical Society, Dr. Aage Kristjansen produced statistics on the treatment of gonorrhea at the Rudolph Bergh Hospital in Copenhagen. In 1937 treatment of gonorrhea with the sulfanilamide group of drugs was instituted, and by the end of June 1939 between 400 and 500 patients had been treated with a Danish preparation of sulfanilamide or the English preparation sulfapyridine. A comparison of the effects of these two preparations was so unfavorable to the former that sulfapyridine has displaced it altogether. While sulfanilamide is apt to be inert early in the disease, sulfapyridine seems to be equally potent whatever the stage of the disease or the sex and age of the patient. Sulfapyridine possesses the further advantage of inflicting fewer and less serious complications and manifestations of drug intolerance than sulfanilamide. Now that a recent attack of gonorrhea can be more readily cured under ambulatory conditions, the claims on hospital beds for the treatment of gonorrhea have dwindled enormously. In 1930 about 59 per cent of the 180 beds in the Rudolph Bergh Hospital were required for the treatment of venereal disease, whereas at present only 10 per cent are required for this purpose. This decline cannot be credited exclusively to the sulfanilamide group of drugs, for bismuth compounds have also played a part in reducing the number of patients requiring hospital treatment for syphilis.

## BUENOS AIRES

*(From Our Regular Correspondent)*

Oct. 14, 1939.

### Cultural Relations with the United States

The number of Argentine physicians and members of other scientific professions who go to the United States for postgraduate studies has increased during the last few years, especially through Professor Houssay's influence. The number is increasing still more because of present conditions in Europe. The main difficulty is the increased rate of exchange, which makes the cost of living and the expense of the trip very high. Requests have been made of American steamship companies to make special reductions for students, such as are allowed them by English, Italian, German and French steamship companies; namely, a reduction of 25 or 50 per cent. However, no reduction is allowed on American ships. The number of persons who may go to the United States with Argentine scholarships is not more than twelve a year. They have scholarships from the Comisión Nacional de Cultura, Asociación Argentina para el Progresso de las Ciencias and Academia Nacional de Medicina. They are persons who are devoted to research or to teaching and who had secured positions on their return home. Argentineans who have been sent to foreign countries with scholarships have obtained important positions in Argentina, such as professors in faculties, heads of laboratories or of some national institution. A reduction in the cost of the trip would aid the financial condition of students.

### Medical Congresses

During the present year the Academia Nacional de Medicina of Buenos Aires held a monthly meeting for the discussion of allergy. Official speakers were Prof. A. Sordelli (who discussed classification of phenomena of allergy and hypersensitivity), Prof. B. A. Houssay (physiologic mechanisms of allergy), Prof. A. Bachmann (allergy and anaphylaxis) and Prof. P. I. Elizalde (pathologic anatomy). Drs. P. Baliña, Segura, Argañaraz, Castex, Raimondi, Bullrich, Araoz Alfaro, E. Finochietto, P. I. Elizalde, Peralta Ramos and Cabanne discussed allergy in relation to dermatology, otorhinolaryngology, ophthalmology, renal diseases, asthma, circulatory diseases, tuberculosis, serum sickness, pediatrics, gynecology and obstetrics, and odontology.

The Asociación Médica Argentina held two meetings, at which the official topics were respectively gastrointestinal hemorrhages and adrenal insufficiency. Drs. J. T. Lewis, E. B. del Castillo, E. Hug and M. Soto were official speakers at the second congress.

The Congresso Argentino de Cirugia held its annual reunion October 8-13 under the chairmanship of Dr. Roberto Sole. The Brazilian delegation was represented by Drs. A. Monteiro and J. Gudin. Drs. Garcia Valenzuela and Vargas Molinare, of Chile, and Ramon Doria, of Paraguay, also were present. The first official topic was "calculi of the biliary tract." Official speakers for the first topic were Prof. E. Blanco Acevedo, of Montevideo, and P. Mirizzi, of Córdoba. Drs. A. J. Bengolea, Velasco Suarez, D. del Valle and I. M. Allende read papers. Bengolea, who reviewed 972 operative cases, emphasized that special consideration should be given to the preoperative period. He advises against routine cholecystectomy and uses frequently the Kehr tube. Prof. P. Mirizzi performs, as a routine procedure, cholangiography during operation with the aim of determining the position of calculi. He advised supraduodenal choledochotomy for removing the calculi from the common bile duct. In many cases he sutures the common bile duct without any drainage. The satisfactory results of operations in biliary calculosis obtained by Professor Mirizzi are well known. He does not believe in unnecessary delay before performing an operation in cases of calculous occlusion of the common bile duct. Professor Mirizzi recently published a book on the functions of the biliary tract. He states that cholangiography shows that in the functions of the biliary tract three different sphincters are concerned: Oddi's, the sphincter of the gallbladder and that of the hepatic duct, which exists immediately above the joint between the cystic and the hepatic ducts.

Profs. Eduardo Villa and Jose Puente discussed the second official topic, varices. Prof. E. Cornejo Saravia (a pupil of Prof. Pedro Chutro) was the speaker for the third official topic, treatment of malleolar and supramalleolar fractures. Surgical demonstrations were performed in all hospitals of Buenos Aires for three days.

### Tendencies in Sanitation

Several subjects relating to the organization of medicine and sanitation were discussed at the Congress of Sanitation, recently held in Santa Fe. The following motions were approved: autonomy of the main department of hygiene, permanent positions for the technicians in sanitation, full time for the personnel working in sanitation, recognition of professional dangers, jubilation and retirement, extension of prenuptial certificates of health to women, and maintenance of medicine. It was resolved to organize the Congreso de la Asistencia Social, which will be held next year in Rosario.

### Personals

Prof. J. J. Spangenberg was recently appointed, by the government, president to the Departamento Nacional de Higiene and to the Comisión de asilos y hospitales regionales.

Dr. Juan Bacigalupo was appointed professor of parasitology at the Faculty of Medicine of Buenos Aires. He will occupy the chair vacated by Dr. D. Greenway, who reached the age limit.

Prof. Jose Arce gave a lecture of farewell from his chair of surgical clinic, which he intended to resign, after which he decided to remain.

Dr. Atilio Costa was appointed professor of surgical technic at the Faculty of Medicine of Buenos Aires.

The following persons were presented with scholarships: Dr. Flaminio Vidal, a scholarship from the Rockefeller Foundation, to work with Dr. S. W. Ranson, of Chicago, on neurology, anatomy and physiology. Miss Inés López Colombo de Allende, a scholarship from the Asociación Argentina para el progreso de las ciencias, to work with Dr. G. W. Corner, of Rochester, N. Y., on sexual endocrinology of primates. Dr. E. de Robertis, a scholarship from the Academia Nacional de Medicina, to work with Dr. William Bloom, of Chicago, on histology. J. Llacer, a scholarship from the Asociación Argentina para el progreso de los ciencias, to work with Professor Benedetti-Pichler, of New York, on microchemistry.

Drs. B. A. Houssay, P. Belou and J. Arce recently celebrated their thirtieth and twenty-fifth anniversaries, respectively, as professors.

### Deaths

Dr. G. Bosch Arana, professor of surgical technic at the Faculty of Medicine of Buenos Aires, recently died at the age of 53.

## ITALY

*(From Our Regular Correspondent)*

Oct. 21, 1939.

### Treatment of Inguinal Hernia

Professor Lanzillo, in a lecture recently delivered to the Società napoletana di Chirurgia, reported a technic for radical treatment of inguinal hernia which is based on the principle of making a solid posterior wall to the hernia. An incision is made on the large oblique muscle. The lower flap is passed behind the muscular layer of the small oblique and transverse muscles by means of a series of U stitches and is placed in front of the fascia transversalis. The upper flap together with the small oblique and transverse muscles are placed in front of the lower muscular flap and sutured to the bridge. A wall is thus formed in front of the fascia transversalis. It is made up of four layers, namely the lower flap of the aponeurosis of the large oblique, the transverse and small oblique muscles, and the upper flap of the aponeurosis of the large oblique. The cord, in accordance with the circumstances, may be lodged behind the fascia transversalis, between the fascia and the aponeurosis of the large oblique (which makes the back aspect of the wall newly formed), between the aponeuritic flaps or in the subcutaneous connective tissue. The speaker pointed out the advisability of cutting the epigastric vessels and Hesselbach's ligament, which is near the vessels, in the course of any operation for inguinal hernia.

### Society Reunion

The Accademia delle Scienze Mediche e Chirurgiche met recently at Naples under the chairmanship of Professor Jappelli. Professors Bakunin and Deza-Cauget doubt the possibility of the formation of so-called total or partial blockage of the reticulo-endothelial system in living animals. From a review of the literature and from their experiments they believe that the phenomenon shows impregnation of the reticulo-endothelial system, which may cause a dysfunction of the system without causing absolute suppression of the function. The speakers adopted the name of impregnation of the reticulo-endothelial system for the phenomenon. The speakers studied rabbits which were impregnated with thorium dioxide sol administered intravenously, intraperitoneally or subcutaneously. Some such animals were inoculated with staphylococcus, streptococcus, pneumococcus or tubercle bacilli of the bovine type, whereas others were kept as controls. The results showed that, notwithstanding the fact that the organic resistance of impregnated animals is diminished in comparison to that of the controls, the lesions caused by staphylococcic infection on the tissues are more acute in the latter than in the former. In subcutaneous inoculation the abscess formation takes place earlier in control than in impregnated animals and the toxic phenomena are slower in the former than in the latter. The lesions caused by intravenous inoculation are of the septicopyemic type in control and of a nephrosic and necrotic type in impregnated animals. In the groups of animals inoculated with tubercle bacilli of the bovine type the controls reacted with the common reactions, namely development of typical regional adenopathies. Impregnated animals developed massive infection with extensive lesions at the spleen, lungs, liver and adrenal cortex. Inoculation of tubercle bacilli by the intravenous route caused tuberculous lesions of the same acuteness and in the same time in both controls and impregnated animals. The most acute lesions were those of the lung. Tuberculous inoculations caused acute splenomegaly of the macroscopic and microscopic types of splenic lymphogranulomatosis in impregnated but not in control animals. Large reticulo-endothelial multinucleated cells which are commonly found in splenomegaly do not store thorium dioxide sol. However, the epithelioid cells and Langerhans giant cells of tuberculous granuloma had the substance stored.

Professor Bakunin spoke on surgical treatment of wounds and also on the influence of vitamins A and D on the evolution of wounds. The speaker reported a method which consists in early careful cleansing, preparation of the wound and removal of necrotic tissues no later than six hours after trauma, suture of any break in the continuity of the tissues (which may be covered with skin) and reduction of fractures or luxations, if any. The limb must be placed at rest, in an inclined plane, to improve the condition of circulation. It must be placed on sterilized cloth and put in a special wire device which is covered with gauze. The cloth and sterilized gauze are changed at intervals and all fluids eliminated are removed. Cod liver oil is applied to the wound every two or three days by means of a siphon bottle. The wound is free from direct contact with any medication as though it were enclosed in a chamber. The method is applied to wounds and burns. It is economical, easy and efficacious. Wounds or burns quickly heal with rapid formation of clean healthy tissues, a small elastic scar and never a keloid. The author pointed out that both wounds and burns are more or less extensive local lesions which cause pathologic repercussion in the whole system, especially in certain organs or tissues. The most grave organic conditions are those caused by local shock, intoxication from reabsorption of substances which originate in scattered tissues and consequent regeneration of the cells. The anabolic and catabolic changes from trauma have an influence on the whole system. From this point of view one can see that cod liver oil, locally applied, acts directly on the focus and indirectly on the general condition. The efficacy of the treatment is due to vitamins A and D in cod liver oil and probably also to some other substance contained in it.

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## *Marriages*

JULIAN LOMBARD, New Orleans, to Miss Bess C. Sheppard of Dallas, Texas, in New York, October 14.

JOHN FAULKNER RAINEY, Greenville, S. C., to Miss Caroline Freeman Stringer of Anderson, October 28.

SIDNEY M. REICH, Wilkes-Barre, Pa., to DR. SYLVIA J. RUBENSTONE of Philadelphia, October 7.

JULIUS LIPSON, Otisville, N. Y., to Miss Netty D. M. Blok of The Hague, Netherlands, October 6.

HOWARD S. REID, Cohasset, Mass., to DR. NANA L. ROSENTHAL of Des Moines in October.

GEORGE TOLSTOI, Washington, D. C., to Lenore Oslander of Uniontown, Pa., September 10.

J. ELLIOTT ROYER, Oakland, Calif., to Miss Helen Hay in Reno, Nev., in September.

# Deaths

**James E. Sadlier** ✠ Poughkeepsie, N. Y.; Albany Medical College, 1887; member of the House of Delegates of the American Medical Association, 1909-1910, 1929-1932; member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons; fellow of the American College of Surgeons; past president of the Medical Society of the State of New York; medical director of a hospital bearing his name; attending surgeon to St. Francis Hospital; consulting surgeon to the Butterfield Memorial Hospital, Cold Spring, Northern Dutchess Health Service Center, Rhinebeck, and the Sharon (Conn.) Hospital; aged 74; died, October 9, of arteriosclerotic heart disease and coronary occlusion.

**Willard Burr Soper** ✠ New Haven, Conn.; Columbia University College of Physicians and Surgeons, New York, 1908; associate professor of medicine at Yale University School of Medicine; member of the Association of American Physicians and the American Clinical and Climatological Association; fellow of the American College of Physicians; served during the World War; medical director of the William Wirt Winchester Hospital, West Haven, a tuberculosis unit of the New Haven Hospital; aged 56; died, October 30, in the New Haven Hospital of brain tumor.

**Patrick Chalmers Jameson** ✠ Brooklyn; Long Island College Hospital, Brooklyn, 1892; member of the American Academy of Ophthalmology and Otolaryngology and of the American Ophthalmological Society; fellow of the American College of Surgeons; surgeon to the Brooklyn Eye and Ear Hospital, St. John's Hospital, Caledonian Hospital, Brooklyn Hospital and House of St. Giles the Cripple; aged 72; died, October 27, in the Long Island College Hospital of duodenal ulcer, pyloric stenosis and gastro-enterostomy.

**James Lyons Cobham** ✠ Jersey City, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1917; fellow of the American College of Surgeons; assistant instructor in surgery at the New York Medical College and Flower Hospital from 1932 to 1935; consulting surgeon at the New Jersey State Hospital, Greystone Park; served during the World War; president of the medical staff of the Christ Hospital; aged 44; died, October 9, of coronary occlusion.

**James E. Murphy** ✠ Hartford, Conn.; Medico-Chirurgical College of Philadelphia, 1909; member of the American College of Chest Physicians; for many years resident physician to the Wildwood Sanatorium; on the staffs of the Manchester (Conn.) Hospital, Hartford Municipal Hospital and the Hartford Hospital, where he died, October 31, of staphylococcic septicemia, osteomyelitis of the cervical spine and perinephric abscess, aged 61.

**Walter Lee Munro** ✠ Providence, R. I.; Harvard Medical School, Boston, 1885; an Affiliate Fellow of the American Medical Association; fellow of the American College of Surgeons; consulting surgeon to the Rhode Island Hospital, St. Joseph's Hospital and the Miriam Hospital, Providence, and the Memorial Hospital, Pawtucket; aged 82; died, October 23, in the Jane Brown Hospital.

**Clarence Whittemore,** Johnson City, N. Y.; Jefferson Medical College of Philadelphia, 1913; member of the Medical Society of the State of New York; fellow of the American College of Surgeons; for many years member of the board of education; on the staff of the Charles S. Wilson Memorial Hospital; aged 48; died, October 23, of heart disease.

**Henry Esson Young,** Victoria, B. C., Canada; McGill University Faculty of Medicine, Montreal, Que., 1888; past president of the Western Branch of the American Public Health Association; provincial officer of health; at one time Provincial Minister of Education and Provincial Secretary; aged 72; died, October 24, in a local hospital.

**George Myrtle Culver** ✠ Jersey City, N. J.; Bellevue Hospital Medical College, New York, 1894; past president of the Hudson County Medical Society; for many years member of the board of education; member and at one time president of the staff of St. Francis Hospital; aged 73; died, October 19, of cerebral embolism and arteriosclerosis.

**Stephen Henry Besley** ✠ Salt Lake City; Northwestern University Medical School, Chicago, 1924; aged 49; surgeon to the Utah State Prison and the Salt Lake County General Hospital; on the staff and member of the board of governors of the Holy Cross Hospital, where he died, October 7, of gallstones with multiple liver abscesses.

**William Hasbrouck Snyder** ✠ Newburgh, N. Y.; New York Homeopathic Medical College and Hospital, New York, 1895; member of the American Urological Association; past president of the Orange County Medical Society; at one time health officer; aged 66; died, October 17, in Rutherford, N. J., of coronary occlusion.

**Herman Frederick Thulin** ✠ Denver; University of Nebraska College of Medicine, Omaha, 1900; on the staffs of St. Luke's Hospital, St. Anthony's Hospital, St. Joseph's Hospital, Children's Hospital, Presbyterian Hospital, Mercy Hospital and the Porter Sanitarium and Hospital; aged 62; died, October 17.

**Nels Christian Nelson** ✠ Cheyenne, Wyo.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; for many years on the staff of the Laramie County Memorial Hospital; aged 66; died, October 15, in the Boulder (Colo.) Sanitarium of carcinoma of the pancreas.

**Ervin Lyman Matthews,** Morrilton, Ark.; University of Arkansas School of Medicine, Little Rock, 1908; member of the Arkansas Medical Society; past president of the Conway County Medical Society; served during the World War; on the staff of St. Anthony's Hospital; aged 54; died, October 17, of pneumonia.

**Frederick Gretton Brathwaite,** New York; College of Physicians and Surgeons, Medical Department of Columbia College, New York, 1890; associate medical director of the Equitable Life Assurance Society; aged 71; died, October 30, in the Stamford (Conn.) Hospital of lobar pneumonia and myocarditis.

**Frederick Adrian Kinch** ✠ Westfield, N. J.; College of Physicians and Surgeons, Medical Department of Columbia College, New York, 1882; formerly secretary of the Union County Medical Society; president of the board of health; aged 79; died, October 25, of myocarditis and arteriosclerosis.

**Aloysius Robert Holdenried,** St. Louis, Mo.; St. Louis University School of Medicine, 1926; member of the Missouri State Medical Association; on the staffs of the Firmin Desloge Hospital, St. Mary's Hospital and the Deaconess Hospital; aged 38; died, October 14, of pulmonary tuberculosis.

**Albert Edwin Hayes** ✠ Cranston, R. I.; Harvard Medical School, Boston, 1898; for many years on the staff of the Rhode Island Hospital, Providence; aged 72; died, October 26, at the Day Kimball Hospital, Putnam, Conn., of cerebral embolism and injuries received in an automobile accident.

**James Da Costa Highsmith** ✠ Fayetteville, N. C.; Jefferson Medical College of Philadelphia, 1918; member of the Southeastern Surgical Congress; fellow of the American College of Surgeons; superintendent of the Highsmith Hospital; aged 49; died, October 18, of coronary occlusion.

**Edward Ludwig Paulsen,** Minneapolis; University of Minnesota Medical School, Minneapolis, 1909; member of the Minnesota State Medical Association; fellow of the American College of Surgeons; on the staff of the Deaconess Hospital; aged 56; died, October 7, of cerebral hemorrhage.

**Arley John Ostrander,** Cave Junction, Ore.; Minneapolis College of Physicians and Surgeons, Medical Department of Hamline University, 1908; on the staff of the Veterans Administration Facility; aged 59; died, October 15, of an accidental gunshot wound inflicted while cleaning a gun.

**Jacob Charles Rothenburg,** Springfield, Minn.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1885; member of the Minnesota State Medical Association; formerly on the staff of St. John's Hospital; aged 79; died, October 16, of coronary occlusion.

**Will H. Moore** ✠ Valley City, N. D.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1903; past president of the North Dakota Health Officers Association; aged 63; died, October 20, in a hospital at Fargo.

**Julius Emanuel Isaacson** ✠ New Orleans; Tulane University of Louisiana School of Medicine, New Orleans, 1918; aged 44; served in various capacities on the staff of the Hotel Dieu, Sisters' Hospital, where he died, October 17, of coronary thrombosis.

**William Henry Forbes,** Poughkeepsie, N. Y.; Indiana Medical College, Indianapolis, 1877; Jefferson Medical College of Philadelphia, 1879; aged 88; died, October 5, in the Vassar Hospital of hypostatic pneumonia and traumatic fracture of the hip.

**John Edward Farrell** ✠ Waterbury, Conn.; University and Bellevue Hospital Medical College, New York, 1903; served during the World War; aged 62; on the staff of St. Mary's Hospital, where he died, October 30, of myocarditis.

**Karl Fischel** ✠ Saranac Lake, N. Y.; Medizinische Fakultät der Universität, Wien, Austria, 1901; superintendent and medical director of the Will Rogers Memorial Hospital; aged 62; died, October 29, of coronary occlusion and arteriosclerosis.

**Wilson H. Thompson,** Celina, Ohio; Marion-Sims College of Medicine, St. Louis, 1899; Cleveland University of Medicine and Surgery, 1901; member of the Ohio State Medical Association; aged 61; died, October 19, of cerebral hemorrhage.

**Frederick William Edelmann,** Saginaw, Mich.; Bellevue Hospital Medical College, New York, 1885; at one time city health officer; for many years police surgeon; aged 75; died, October 23, in St. Mary's Hospital of carcinoma of the larynx.

**Theodore Grady Gaskins** ✠ Mount Vernon, N. Y.; Medical College of Virginia, Richmond, 1929; on the staff of the Mount Vernon Hospital; aged 35; died, October 30, of an accidental gunshot wound inflicted while cleaning a gun.

**Claude Bradbury Parker,** Gallipolis, Ohio; Medical College of Ohio, Cincinnati, 1895; member of the Ohio State Medical Association; aged 65; died, October 30, in the Holzer Hospital of cerebral hemorrhage.

**David Nathan Hopkins,** Friendship, Ohio; Cincinnati College of Medicine and Surgery, 1898; member of the Ohio State Medical Association; aged 70; died, October 31, in the Mercy Hospital, Portsmouth.

**Malcolm Lale Samms,** New Orleans; Kentucky School of Medicine, Louisville, 1901; on the staff of the Veterans Administration; served during the World War; aged 62; died, October 30, of heart disease.

**Clyde Jacob Munns** ✠ Newburgh, Ind.; Kentucky School of Medicine, Louisville, 1908; county health officer; aged 54; died, October 24, in the Welborn-Walker Hospital, Evansville, of abdominal carcinomatosis.

**Fannie Herriott Kellogg,** New Rochelle, N. Y.; New York Medical College and Hospital for Women, 1882; aged 82; died, October 9, of cerebral hemorrhage, hypostatic pneumonia and arteriosclerosis.

**Martha Bell Moorhead** ✠ Minneapolis; Woman's Medical College of Pennsylvania, Philadelphia, 1892; an Affiliate Fellow of the American Medical Association; aged 73; died, October 13, of bronchopneumonia.

**Carl Daniel Kolset,** Sanborn, Minn.; Medical Department of Hamline University, Minneapolis, 1905; served during the World War; aged 63; died, October 18, of bronchopneumonia and chronic encephalitis.

**Myer Mordecai Pinsky,** Camden, N. J.; University of Maryland School of Medicine, Baltimore, 1925; member of the Medical Society of New Jersey; aged 38; died, October 6, of coronary thrombosis.

**Eugene Ziegler Hillegass,** Mantua, N. J.; Jefferson Medical College of Philadelphia, 1880; member of the Medical Society of New Jersey; aged 85; died, October 8, of coronary thrombosis.

**John Joseph Dooling,** Malverne, N. Y.; Long Island College Hospital, Brooklyn, 1899; surgeon to the police and fire departments; aged 64; died, October 3, of carcinoma of the lung.

**Bertram A. Martin,** Mineral, Ill.; Northwestern University Medical School, Chicago, 1893; aged 69; died, October 30, in the J. C. Hammond City Hospital, Geneseo, of heart disease.

**Joseph B. Chambers,** Los Angeles; Manitoba Medical College, Winnipeg, Man., Canada, 1898; aged 83; died, September 22, of arteriosclerosis, hypertension and cerebral hemorrhage.

**Wallace Andrew Aitken,** Enid, Okla.; Washington University School of Medicine, St. Louis, 1901; served during the World War; aged 62; died, October 15, of uremia and nephritis.

**Thomas K. Shields,** Wheeling, W. Va.; University of Maryland School of Medicine, Baltimore, 1890; aged 74; died, October 7, of chronic nephritis, myocarditis and arteriosclerosis.

**Thomas Owen Crawford** ✠ Dewey, Okla.; Denver and Gross College of Medicine, 1910; superintendent of health of Dewey; aged 66; died, October 20, of pneumonia.

**William Henry Kendrick,** Tulsa, Okla.; Hospital College of Medicine, Louisville, Ky., 1897; aged 77; died, October 22, of hypertension, myocarditis and cerebral infarct.

**Jefferson Martain Colburn** ✠ Riverside, Calif.; Kansas City (Mo.) Homeopathic Medical College, 1895; aged 81; died, September 15, of herpes zoster.

**Avery Kirk Brodie,** Derby, N. Y.; University of Buffalo School of Medicine, 1899; aged 66; died, October 4, of coronary occlusion and arteriosclerosis.

**Richard Edward Banks,** Washington, D. C.; Howard University College of Medicine, Washington, 1927; aged 50; died, October 16, of cerebral hemorrhage.

**Alexander Curtis Elinor,** McKenzie, Tenn.; Memphis Hospital Medical College, 1912; aged 64; died, September 15, of diabetes mellitus and hypertension.

**George Frederick Martin,** Corydon, Ind.; Hospital College of Medicine, Louisville, Ky., 1884; aged 80; died, October 20, of carcinoma of the stomach.

**John Henry Martin** ✠ Binghamton, N. Y.; University of the City of New York Medical Department, 1877; aged 85; died, October 4, of myocarditis.

**Mary Sophia Ross,** Hannibal, Mo.; Rush Medical College, Chicago, 1908; aged 72; died, October 5, in Central Bedeque, Prince Edward Island, Canada.

**James Madison Godwin,** High Point, N. C. (licensed in North Carolina, year unknown); aged 79; died, October 13, of carcinoma of the mastoid.

**Thomas Martin Eaton,** Viola, Tenn.; Vanderbilt University School of Medicine, Nashville, 1884; aged 84; died, October 4, of influenza and senility.

**George Lounsbery,** Huntington, W. Va.; New York Homeopathic Medical College, 1878; aged 84; died, October 13, of pneumonia.

**William Edgar Hardman,** Annona, Texas; Missouri Medical College, St. Louis, 1889; aged 78; died, September 14, of diabetes mellitus.

**Zachariah Garton Jones,** Downey, Calif.; Kansas City (Mo.) Medical College, 1905; aged 55; died, September 19, of angina pectoris.

**Henry Edward Pastor,** Petaluma, Calif.; California Medical College, Oakland, 1894; aged 83; died, September 28, of heart disease.

**John Sutherland Douglas,** Halifax, N. S., Canada; University of Toronto Faculty of Medicine, 1916; aged 46; died, October 26.

**Harvey Almond Hill,** Amarillo, Texas; Rush Medical College, Chicago, 1898; aged 66; died, October 25, of carcinoma of the liver.

**Alma Kruemcke,** San Antonio, Texas (licensed in Texas, under the Act of 1907); aged 69; died in October of cerebral hemorrhage.

**Horace Cooper Wrinch,** Vancouver, B. C., Canada; Trinity Medical College, Toronto, Ont., 1899; aged 73; died, October 19.

**Finlay Munroe,** Paris, Ont., Canada; McGill University Faculty of Medicine, Montreal, Que., 1913; aged 50; died, October 27.

**William Herbert Bell,** Cincinnati; Miami Medical College, Cincinnati, 1886; aged 79; died, October 21, of bronchopneumonia.

**Walter N. Thomas,** Chicago; Reliance Medical College, Chicago, 1909; aged 59; died, October 18, of coronary occlusion.

**Perry Jacob Shank,** Cincinnati; Miami Medical College, Cincinnati, 1902; aged 80; died, October 25, of chronic myocarditis.

**Jessie B. Conway,** Los Angeles; Denver Homeopathic College, 1897; aged 77; died, September 10, of pernicious anemia.

**Richard Beck Chapman,** Laguna Beach, Calif.; Cooper Medical College, San Francisco, 1896; aged 65; died, September 22.

**Clarkson P. Hockett,** Spiceland, Ind.; Curtis Physio-Medical Institute, Indianapolis, 1893; aged 72; died, September 27.

**Joseph Wilkinson,** Regina, Sask., Canada; Manitoba Medical College, Winnipeg, 1897; aged 74; died, September 17.

**Maura Bridget Flynn,** Brooklyn; National University of Ireland, Dublin, 1924; aged 38; died, September 26.

**Lebbeus Burton Schneider** ✠ Troy, N. Y.; Albany Medical College, 1898; aged 62; died, September 19.

# Correspondence

## "CLINICAL GASTROENTEROLOGY"

*To the Editor:*—I wish to call attention to the review of my book "Clinical Gastroenterology," published in the September 2 issue of THE JOURNAL.

The reviewer states that "the text is amply illustrated. However, many of the x-ray films are obsolete, as evidenced by the presence of a ring to denote the position of the umbilicus on the plate. These, as the author does not state, are some of the older films of the late R. Walter Mills."

This statement is absolutely false for the following reasons:

On pages 60, 126, 150 and 240 it is definitely stated that the films are taken from Dr. Mills's original work.

On page 274 the films are taken according to Mills's original method of using small cylinder compression over the gallbladder region, and due credit is given him in the text.

Furthermore, I have never discontinued the use of the ring to locate the position of the umbilicus. This method is also being employed by many radiologists; therefore it is not true that the use of this ring indicates that the films are obsolete.

HORACE W. SOPER, M.D., St. Louis.

## POLIOMYELITIS AFTER ADENOTONSILLECTOMY

*To the Editor:*—The subject of poliomyelitis following adenotonsillectomy is one of such importance that I submit the following tabulation of cases from the literature as a supplement to Dr. Felderman's letter in your issue of October 28. No case has been included in which the interval between operation and the onset of poliomyelitis was more than twenty-two days. The references will all be found in Stillerman and Fischer's paper (*Am. J. Dis. Child.* **56**:778 [Oct.] 1938) except the one to the more recent paper of Koskoff, Amshel and Lebeau (*Arch. Pediat.* **56**:19 [Jan.] 1939). The recent cases reported by Ayer and by Aycock are mentioned by Stillerman and Fischer as obtained by personal communication:

| | Cases | Bulbar |
|---|---|---|
| Ayer (1928) | 9 | 9 |
| Aycock and Luther (1929) | 16 | 11 |
| Silverman (1931) | 5 | 4 |
| Stillerman and Fischer (1938) | 13 | 9* |
| Aycock (1938) | 2 | 2 |
| Ayer (1938) | 6 | 6 |
| Eley and Flake (1938) | 20 | 17 |
| Koskoff, Amshel and Lebeau (1939) | 2 | 2 |
| Total | 73 | 60 (82%) |

* Including two cases of encephalitis.

As Stillerman and Fischer point out, the proportion of bulbar cases in poliomyelitis after adenotonsillectomy is so much higher than in poliomyelitis generally that the chances of its being accidental are statistically negligible (fifteen in 10,000 in their own series, in which the proportion is lower than in the totals of the compilation given in the tabulation). There seems to be little doubt that the operation provides a portal of entry through the traumatized cranial nerves supplying the tonsillar fossa and the nasopharynx to virus already present in that region. The studies of A. B. Sabin (Experimental Poliomyelitis by the Tonsillopharyngeal Route, THE JOURNAL, Aug. 13, 1938, p. 605) give experimental support to this contention.

HAROLD K. FABER, M.D., San Francisco.

## LOST PATIENTS FROM AN OUTPATIENT CLINIC

*To the Editor:*—In THE JOURNAL of September 9, page 1037, appeared an article captioned "Lost Patients from an Outpatient Clinic" by Horace Gray, M.D., and Margaret Curtis, R.N. The report was made to determine the percentage of patients who could be persuaded to return to the clinic. The follow-up mailing system was used for this purpose.

The summary showed that the "clinic fails" amounted to 14 per cent, and the writers bemoaned the fact that from the point of view of social economy the results were most discouraging. Is it possible that the time spent by the clerical force on these patients is stretching the humanitarian purposes of dispensary work too far? This leads me to answer in the affirmative. Moreover, the present social system has a tendency to humor patients, often leading them to believe that the benefits derived are wholly shared by the dispensary physicians. In this assumption the outpatient patrons cannot be entirely blamed. The social service department, to justify its existence, must necessarily encourage a large active attendance of outpatients. The social worker makes it a point to cater to the whims of the patients in the same manner that a manager does to a temperamental metropolitan opera star.

I have had twenty years of clinical work and in my experience patients who apply for free treatment are those who feel that the best specialists can be found in hospitals. Moreover, they are under the impression that dispensary physicians are paid officials.

There are many reasons why patients fail to return to the clinic. First, the economic status of the family might have improved—a fact not disclosed in the follow-up system of Gray and Curtis. Of course lame excuses such as that the patient could not wait, that home duties interfered with treatment or that their automobile was not in working condition are but a few that account for the clinic "fails."

It would be considered somewhat gauche from an ethical point of view if a physician were to write a letter to his private patient asking him why he did not return for treatments. The patient would question the motive and his suspicions would be unduly aroused. The same sort of reasoning prevails with clinic patients.

Of course, ambitious social service workers and superintendents of hospitals devise ways and means of writing to patients so that the roll of clinic admissions can be lengthened. The same group has inspired the story about hospital costs and inadequate care of the sick in this country.

Some of the physicians engaged in the dispensary work feel that if the superintendents or social workers had their way they would install private cubicles for patients and have them enter or leave the place in some sort of disguise so that they would not be recognized. It has also been suggested that patients who are great lovers of music should have some sort of symphonic entertainment while waiting for treatment. It would help to chase away the tedium of monotony. Motion pictures too have their place.

I believe that the selfless idea of free treatments in the outpatient departments is overstressed, and physicians are opposed to have these patients brought back by postcard or telephone, no matter how scientifically interesting their conditions may be.

I strongly believe that 60 per cent of the patients admitted to the dispensary can well afford private treatment and that by crowding out the 40 per cent who are deserving of free treatments and who require no reminders they are jamming up the hospital machine.

If it is not ethical for a physician to solicit a patient, neither should it be the prerogative of a social worker to coax patients back to the outpatient clinic.

LEON FELDERMAN, M.D., Philadelphia.

# Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

## CHOICE OF TREATMENT IN PNEUMONIA

*To the Editor:*—**About two years ago a woman aged 62 had pneumonia of the right lower lobe. Because of lack of typing facilities she was given combined types I and II serum and also sulfanilamide totaling about 30 Gm. After about five days she complained of pain in the right upper quadrant and over the liver and lower part of the chest. Jaundice then appeared, and it was felt that she had hepatitis. Sulfanilamide as the cause was questioned, first because of the small total dose and second because of previous gallbladder (and liver?) dysfunction. Furthermore the pneumonia, which was in the right lower lobe, might have been contributory. After prolonged dextrose and oxygen therapy she recovered. Later she proved to have had type VII pneumonia. My questions are: 1. If this patient contracts pneumonia again, what would be the choice of treatment; sulfapyridine or serum? 2. Is it not true that she may now be sensitive to both? 3. Would there again be danger of hepatitis? 4. Has serum proved to be efficacious in elderly persons? 5. Do not most authorities, thus far, feel that sulfapyridine is, in such cases, apt to bring better results?**

**M.D., Iowa.**

ANSWER.—1. The choice of the appropriate specific treatment for a patient suffering from pneumococcic pneumonia depends on such factors as the condition of the patient's liver, kidneys and blood-forming organs, the type of pneumococcus involved, the time of treatment and the presence of bacteremia, as well as the availability of remedies and of the skills required to use them effectively. All the indications and contraindications for the several available remedies have not been established. Patients suffering from the type III pneumococcus, especially with bacteremia, should receive sulfapyridine. Patients in the early stage of pneumonia of a type for which potent serum is available, if they are insensitive to the kind of serum to be employed, and patients who have failed to produce immunity as evidenced by the spread of the lesion may receive both serum and sulfapyridine advantageously. In the absence of contraindication, sulfapyridine may be given pending the report on laboratory work.

2. It does not follow from her experience that this patient is sensitized to either remedy, sulfapyridine or serum. Sulfapyridine sensitivity is probably not acquired from previous use but is due to vulnerability of tissues. If tissues have been severely injured by a previous administration, it is well not to give the remedy a second time. Patients are not necessarily sensitized by serum and, if sensitized, do not necessarily retain their sensitization for two years after the administration of either horse or rabbit serum. If the patient has become sensitized to a serum, serum from a different animal source may be employed or, if necessary, even from the same source by the method of inducing a refractory phase and antianaphylaxis, described by J. G. M. Bullowa (The Management of the Pneumonias for Physicians and Medical Students, New York, Oxford University Press, 1937, p. 309). There is no evidence that sulfanilamide sensitizes patients to sulfapyridine or that sulfapyridine cannot be used advantageously in a second attack of pneumonia after the first has been treated with that drug.

3. There is insufficient evidence presented for one to assert that this patient had hepatitis. Some hepatic damage may have resulted from the use of sulfanilamide or from her disease, or there may have been simultaneous cholelithiasis. It would be helpful to know the depth of the jaundice or whether blood phosphatase was increased.

4. Ample early doses of specific serum have been efficacious in the treatment of old persons suffering from pneumococcic pneumonia.

5. Some authorities feel that both serum and sulfapyridine should be used in the severe infections of old persons unless there is a specific contraindication for one or the other. Recovery from pneumonia ultimately depends on the operation of immunity factors, and in older persons the immunity mechanism may be feeble. Serum hastens the advent of an excess of antibody, which is required to neutralize specific capsular carbohydrate and to induce both phagocytosis and lysis. Sulfapyridine inhibits or kills pneumococci, provided an adequate concentration for the pneumococcus present is maintained for a sufficient length of time. The use of serum with sulfapyridine decreases the amount of sulfapyridine and of serum required. Old persons may suffer from azotemia after dosage with sulfapyridine because they frequently have impaired kidneys. Bone marrow function, which is often feeble in the elderly, may be further depressed. No one has had sufficient controlled experience to be authoritative in expressing a preference for either type of treatment in the elderly as opposed to those in other periods of life.

## BLOOD SEDIMENTATION

*To the Editor:*—**What is the simplest blood sedimentation test, what technic is used and what are the normal readings? Does it make any difference whether sodium citrate solution 5 per cent or ammonium oxalate with potassium oxalate is used as long as the blood is prevented from coagulating? Why are both the ammonium and the potassium oxalate used? Would not one of them be enough? Is not use of Wintrobe hemocrit with one of the coagulants as simple and accurate as the Westergren method?**

**M.D., Minnesota.**

ANSWER.—There is some difference of opinion regarding blood sedimentation tests. One of the simplest certainly is the Linzenmeier test. Linzenmeier tubes with calibrations at the 0, 6, 12 and 18 mm. levels are easily procurable and cheap. One and six-tenths cc. of blood drawn from the vein is mixed with 0.4 cc. of 3.8 per cent sodium citrate solution in a small medicine glass or evaporating dish and the tube is filled with the mixture to the 0 mark and allowed to stand upright in a small rack. For women from two to five hours is required for the blood to fall to the 18 mm. level. For men the time required is from three to seven hours.

With regard to the use of anticoagulants, experimental work has shown that sodium citrate solutions in the concentrations used with the Linzenmeier and Cutler technics retard the sedimentation rate considerably. It has been found that the ammonium oxalate and potassium oxalate mixture as devised by Heller and Paul has no effect on sedimentation rate or erythrocyte cell volume. Potassium oxalate in 20 per cent solution may be used alone as the anticoagulant without producing any significant alteration of the sedimentation rate.

Use of the Wintrobe hemocrit with the mixture of ammonium and potassium oxalates as the anticoagulant would probably be as simple and as accurate as the Westergren method.

## ANAPHYLACTIC REACTIONS AND HORSE SERUM

*To the Editor:*—**I am writing to ask your advice as to the quickest and simplest method for skin testing children before administering horse serum. As part of my work as city physician I treat a number of cases of diphtheria, in most of which toxoid has been previously administered. Consequently the diphtheria is quite mild. On occasions I have used an intradermal test with a 1:10 dilution of the serum and have then waited twenty minutes for a reaction. This procedure is time consuming because the syringes in which our antitoxin is supplied have needles which are too large for intradermal use. Consequently it is necessary to sterilize a hypodermic syringe to perform this test. On other occasions I have simply placed one drop of undiluted antitoxin in the conjunctival sac. 1. Have serious accidents ever been known to follow administration of horse serum when the conjunctival test was negative? 2. What test for sensitivity would you recommend under the circumstances mentioned?**

**M.D., Virginia.**

ANSWER.—1. Yes, instances have been recorded in which death resulted from anaphylactic shock following the administration of horse serum to patients whose conjunctival tests for sensitivity had been negative. Unfortunate occurrences of a similar nature have also taken place notwithstanding that intracutaneous sensitivity tests to horse serum were negative.

2. The intracutaneous test for sensitivity which has been used is the one most commonly employed. When the ophthalmic test is performed a dilution of 1:10, as in the case of the intracutaneous test, is perhaps preferable to using undiluted serum. Sometimes a scratch test is made for the purpose of indicating susceptibility to horse serum. For practical purposes, under the conditions described, a scratch test might be sufficient.

As toxoid contains no horse serum and because toxin-antitoxin is used much less frequently than some years ago, it might be expected that fewer serum reactions would result than formerly. On the other hand, because of an increased use of scarlet fever antitoxin a certain number of children may have been sensitized to horse serum on that account. With the improved methods of concentration and refinement, antitoxin serum reactions seem to be much less numerous and far less severe than many years ago.

In some contagious disease hospitals, routine sensitivity tests are made on all patients to whom serum is to be administered. In other contagious disease hospitals no tests are made for sensitivity unless a history of previous serum administration has been obtained or some allergic condition is known to exist. In two contagious disease hospitals in which the latter plan is followed, many thousands of diphtheria patients have been treated without a single instance of an anaphylactic death.

## CHLORAL HYDRATE AND WHISKY

*To the Editor:*—I recently read in Bastedo's Materia Medica, 1938 edition, that chloral hydrate should never be given with alcohol. A patient, after trying everything, gets more satisfaction from 2½ drachms (9.5 cc.) of a chloral preparation at 9 p. m. and 1½ ounces (45 cc.) of whisky in a tumbler of water at 10 o'clock. Is there anything in Bastedo's remarks as quoted that would apply to this? The patient never has to take anything for asthma during the day, but most nights one or two such doses between 10 p. m. and 6 a. m. For ten years he relied on epinephrine.

Nathaniel F. Cheever, M.D., Greenfield, N. H.

ANSWER.—Chloral hydrate should never be administered with alcohol in a prescription. The combination of chloral and alcohol results in the formation of chloral alcoholate, which used to be known as "knock-out drops" and is now termed a "Mickey Finn." Chloral alcoholate is a powerful and rapidly acting cerebral depressant. In prescriptions containing chloral and alcohol, the chloral alcoholate tends to rise to the surface. Without the proper shaking, the danger of acute intoxication from such a preparation is immediately apparent, since the patient receives all of the chloral at the first dose. The preceding remarks do not necessarily apply, however, to the conditions stated in the question. The patient is taking single doses of chloral hydrate with whisky, and the result is better hypnosis and deeper depression. The patient evidently requires this amount of depression to sleep in spite of his asthma and the only harm that can result will be the possible damage to the liver and other parenchymal tissues from the use of chloral hydrate and alcohol.

## MIGRAINE

*To the Editor:*—A 50 year old white man for the past twenty years, with increasing frequency, has had attacks beginning with central blurred vision in the left eye, spreading peripherally and followed almost immediately by similar haziness in the right eye. Vision clears from right to left, completely leaving the right eye first and the lateral half of the left eye last. This phase always lasts exactly twenty minutes and is followed by pain behind the eyeballs which may last anywhere from one to twenty-four hours. The attacks occur at any time of the day, and the patient has even awakened in the morning with typical pain behind the eyeballs. Occasionally the attacks are accompanied by numbness of the hands, lips and tongue. Competent ophthalmologic examination reveals only a slight degree of sclerosis. Routine physical and neurologic examinations show no abnormality. The history is negative for head injury, and there is no family history of migraine, epilepsy or similar disorder. The patient is overweight, and three of his four children show varying degrees of Fröhlich's syndrome. What procedures should be adopted to establish a diagnosis?

M.D., Ohio.

ANSWER.—The diagnosis must be based on the history, as structural changes are unlikely to be found by roentgenograms or even by encephalogram or ventriculogram. The long history, sudden onset of the central scotoma, rapid course, pain behind the eyes, paresthesias of hands, lips and tongue and complete recovery from each periodic attack are typical of migraine. The lack of abnormal ophthalmologic features, absence of family history of migraine or epilepsy and signs of endocrine dysfunction in the children are also consistent with the diagnosis, although a large percentage of patients with migraine have a family history of attacks. Similar cases of migraine will be found in the classic descriptions of the disease as given by Airy, Liveing and others.

References:

Airy, Hubert: On a Distinct Form of Transient Hemiopia, *Phil. Tr., London* **160:** 247, 1870.

Liveing, Edward: On Megrim, Sick-Headache, and Some Allied Disorders, London, J. & A. Churchill, 1873.

## PASSIVE VASCULAR EXERCISE

*To the Editor:*—What information can you give me on the present status of passive vascular exercise or other pressure-vacuum devices for the improvement of the circulation in arterial occlusion? Are any such devices Council accepted? What recent articles have appeared on this subject?

M.D., Minnesota.

ANSWER.—There is a wide difference of opinion relative to the clinical value of passive vascular exercise, a term used to designate alternate periods of suction and pressure applied to an extremity enclosed in some device such as a glass boot. Several such devices are accepted by the Council on Physical Therapy. The evidence that passive vascular exercise significantly increases the circulation to an extremity lacks impressiveness. In fact, there is no conclusive physiologic evidence that the circulation is improved. In spite of this, some physicians who have had wide experience with this method of treatment feel that definite clinical evidence of improvement in the circulation of persons suffering from arterial diseases results from it. Other physicians feel that the benefit noted does not result specifically from this particular treatment but that it is due in large degree to other methods of treatment carried out at the same time and to natural processes of healing and to establishment of collateral circulation. Some physicians believe that passive vascular exercise is valueless. A fair summary of the situation is that the earlier enthusiasm for this treatment has subsided greatly.

References:

Herrmann, L. G.: Passive Vascular Exercises, Philadelphia and London, J. B. Lippincott, 1936.

Allen, E. V., and Brown, G. E.: Intermittent Pressure and Suction, THE JOURNAL, Dec. 21, 1935, p. 2029.

Kountz, W. B., and Smith, J. R.: *Am. Heart J.* **16:** 55 (July) 1938.

Herrmann, L. G., and Reid, M. R.: *Ann. Surg.* **100:** 750 (Oct.) 1934.

## URINARY SEDIMENT

*To the Editor:*—For some time I have been seeing a peculiar sediment in the urine which I cannot identify, and I find no reference to it in any laboratory manual available. It is "black" masses of what appears to be pigment matter, not unlike the calcium bilrubinate pigment in bile. I found them in unusual numbers recently in a specimen showing heavy calcium output with Sulkowich redgent. Examination of the calcium sediment still showed a moderate number of these masses. Could they be calcium and therefore indicate excessive calcium elimination?

S. R. Salzman, M.D., Toledo, Ohio.

ANSWER.—It is almost impossible to give a definite reply as to the character of the "black masses." It might be discolored tyrosine. If so, it should be soluble in dilute alkaline or dilute sulfuric acid solutions. Such solutions, if not too weak or too acid or basic, should give a positive Millon reaction. The black masses might also be melanin. If so, one would expect the urine to be highly colored. The material should be somewhat soluble in alkaline solutions and should then be reprecipitated as brown to black material on addition of acid to the neutral point or slightly beyond. If a few drops of ferric chloride solution added to 100 cc. of urine produce a gray precipitate which darkens on addition of more ferric chloride, it is considered a positive test for melanin. Melanins should not be confused with indigo. If the dark masses are due to indigo, the material should dissolve in chloroform.

## VERTIGO

*To the Editor:*—A patient's chief complaint is vertigo. A few nights ago she awakened to find herself extremely weak, nauseated and dizzy. She turned on the light and attempted to get out of bed, but the vertigo was so severe she was forced to lie down. She described the sensation as feeling "like the room was spinning around." She was so weak that it was an effort to lift her hand. She was given a small drink of whisky and shortly thereafter went to sleep. The next morning she apparently was all right until she got out of bed and walked a short distance, when the vertigo returned again and she had to hold to the wall to keep from falling. She was helped back to bed and after lying down a while felt all right again. The next day while lying on my examining table she suddenly grasped the table and became much alarmed. She said "something like a wind" had passed through her head in the occipital and mastoid regions, and the vertigo had returned again. She complained also of extreme weakness and nausea but did not vomit. She had no ringing in the ears and was not worse on lying on either side. This vertigo continued when the patient was in the erect position for twenty-four hours and then began to subside (during this time the patient was in bed) only to return again when she was up for several hours. Results of physical examination were negative except for a pulse rate of 54 per minute. This increased to 90 per minute during the attack. The blood pressure is 120 systolic and 78 diastolic. The urine and blood counts are normal. A blood Wassermann test is being done. Examination by a nose and throat specialist shows no abnormality except a minor error of refraction. Examinations to determine the condition of the labyrinth were not done. There is no nystagmus. This is apparently a case of pseudo Ménière's disease. I am considering the possibility of brain tumor. What other procedures may be done to make the diagnosis more definite? I have put the patient on a salt-free diet and am administering rather large doses of ammonium chloride. I should like advice on the treatment of such a condition and the prognosis as far as is known.

M.D., Georgia.

ANSWER.—True vertigo always indicates a disturbance of the labyrinth. Such disturbances may be transient functional affairs, organic disease in the labyrinth itself, disease of the nerves such as Ménière's syndrome and disease of the central nervous system at higher levels. Ménière's disease produces vertigo but this diagnosis cannot be safely made from the data given here, although the possibility should be thoroughly investigated. Brain tumor is another possibility.

The treatment of this condition must be based on more accurate diagnosis, and no prognosis can be hazarded until such a diagnosis is made. Tests to determine the cause of vertigo and to localize such causes constitute a rather highly specialized procedure and require an intimate knowledge of cerebral localization. A discussion of this subject, with references to original sources, may be found in most standard textbooks on neurology. Two such works are:

Wechsler, I. S.: A Textbook of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1935.

Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

## VISUAL DISTURBANCE AND SULFANILAMIDE

*To the Editor:*—A white man aged 33 had gonorrheal urethritis and cystitis. Besides the usual local treatment I prescribed sulfanilamide 2.4 Gm. daily for the first week and 1.8 Gm. for the second week. After that time the patient suddenly complained of visual disturbances, which made it impossible for him to drive his car. He was able to read a newspaper when it was brought near to his eyes. There was no headache or any other pain. The next day he had a temperature of 100.4 F. and a skin rash, limited to the face and forearms, which had been exposed to sunlight. The eye examination by an ophthalmologist revealed a definite myopia, which could be completely corrected by means of glasses. There was no ciliary spasm or optic neuritis. Sulfanilamide was interrupted and after five days the patient's eyesight was normal again. He never stopped working. Since I have not found a similar case in the literature concerning sulfanilamide I should like to know whether such a symptom has been observed before.

Manfred Landsberg, M.D., Cudahy, Wis.

ANSWER.—Instances of disturbances of vision in the course of sulfanilamide therapy are quite uncommon. Many patients may complain of difficulty in reading during sulfanilamide therapy, but this in general is due to an inability to concentrate well rather than to any disturbance in vision.

Paul C. Bucy (Toxic Optic Neuritis Resulting from Sulfanilamide, THE JOURNAL, Sept. 25, 1937, p. 1007) reported that a girl with osteomyelitis developed severe disturbances in vision because of a toxic optic neuritis after the administration of a single tablet (0.3 Gm.) of the drug. Four days elapsed before the child's vision was normal. Visual hallucinations have been noted. Temporary myopia has not been described.

## FULGURATION OR DESICCATION OF MOLES

*To the Editor:*—Apropos of the query "Moles and Their Excision" in The Journal, September 16, page 1152, I should like to inquire as to the propriety of removing the moles, particularly the deeply pigmented ones, by means of fulguration, or desiccation. Women particularly are anxious and willing patients for the cosmetic improvement obtained, and while I have had excellent results so far, the thought of malignancy always obtrudes. Naturally, with the high frequency currents the tissue is totally destroyed (sufficiently beneath the corium), making pathologic study obviously impossible. Excision would leave scars. M.D., New York.

ANSWER.—The question of fulguration, or desiccation, of pigmented moles is to some degree controversial. Many physicians are of the opinion that this procedure is effective and without danger. This opinion is based on the treatment of large numbers of lesions by such methods without apparent complications. Another school believes that desiccation, or electrocoagulation, of pigmented moles is accompanied by the possibility of dissemination of the disease. This opinion is based on the clinical observation of patients who have been treated in this manner and who developed fully malignant melanomas in the treated areas. Numerous authorities on this question are of the opinion that the safest therapeutic procedure for a pigmented mole which is subjected to irritation or which is showing changes suggestive of malignant degeneration is careful, wide surgical removal.

## TIGHT FORESKIN AND CIRCUMCISION

*To the Editor:*—In the newborn male child what is the best method of dealing with a tight foreskin of the penis? Is circumcision or just nicking, thus retracting it, the best measure? M.D., Pennsylvania.

ANSWER.—It is generally considered that the tight foreskin at birth may be safely let alone provided there is ample room for urination. If it is necessary because of blockage of the stream to make an opening, this can be done by breaking up the adhesions and retracting the foreskin or by circumcision, the choice of which procedure should rest with the family.

In most instances with tight foreskin if the physician and mother will be patient, retraction can be done after several months as a gradual procedure without any operation at all.

## NITRAZENE TEST OF SALIVA

*To the Editor:*—Of what value is the nitrazene test of saliva in determining the body $p_H$? Dr. Walter B. Guy, of Florida, suggests using a cantharides plaster for eight hours and then determining the $p_H$ from the plasma by means of phenol red. In making this test is it the aqueous or the alcoholic phenol red which is used as the indicator? Is there any special color chart to use? How reliable is this test?

Henry B. Hibbe, M.D., Dubuque, Iowa.

ANSWER.—The nitrazene test is a rough test for the $p_H$ of body fluids. The phenol red test, if properly applied, is more accurate. The phenol red solution is prepared by grinding in a mortar 0.03 Gm. of pure dye with 0.86 cc. of tenth normal sodium hydroxide and diluting the final solution to 100 cc. with distilled water. To apply the test, collect about 5 cc. of saliva by expectorating into a test tube containing 2 cc. of neutral liquid petrolatum. Take 4 cc. of the saliva and add 0.2 cc. of the phenol red indicator solution. It is best to compare the color with standards of different $p_H$ values containing the same amount of phenol red. A color chart is published by William Clark in his Determination of Hydrogen Ion Concentration.

## LUDWIG'S ANGINA

*To the Editor:*—Is there any evidence that Ludwig's angina ever assumes epidemic proportions? Particularly in the experience of the late World War was it more common except in the presence of oral injuries? In operating room technic is it considered more infectious than the ordinary pyogenic infections? M.D., Pennsylvania.

ANSWER.—No evidence has been found that Ludwig's angina ever assumes epidemic proportions. While cervical cellulitis was common in the World War, Ludwig's angina was not and did not commonly complicate oral injuries. The causative organisms vary and are not regarded with any more concern in the operating room than any other acute infection.

## NO HEREDITARY FACTOR IN FACIAL PARALYSIS

*To the Editor:*—A 35 year old housewife has a right peripheral facial paralysis. The etiology has been determined as exposure to an open window. The patient's father and older brother at one time in their lives also had attacks of peripheral facial paralysis. Can you tell me whether there is a form of familial peripheral facial paralysis and, if there is, can you tell me where I can find the articles describing it?

M.D., New York.

ANSWER.—It is not believed that the facial paralysis in such cases has anything to do with familial periodic paralysis or any other familial disease. The disorder is so common that it might easily happen to affect several members of a family.

## FEVER FOR BRONCHITIS AND ASTHMA

*To the Editor:*—Would fever cabinet treatments be of any value in chronic bronchitis and asthma? Has sulfanilamide been used in this condition.

M.D., Illinois.

ANSWER.—The fever treatment for asthma was tried originally for severe intractable cases. Even for these, it has now been generally discarded as too severe a form of management for the results obtained. Sulfanilamide has not been tried for this condition. There seems to be no adequate basis for its trial.

## WOOL SENSITIVITY IN WOOLEN INDUSTRY

*To the Editor:*—Do you know of any particular treatment the woolen manufacturers use on their employees that are allergic to wool?

M.D., Michigan.

ANSWER.—The only two methods that can be used in wool sensitive cases are avoidance of contact or minimizing contact with virgin wool, and hyposensitization. The former is far preferable to the latter. It is hardly possible to decrease the amount of wool dust in wool manufacturing establishments. No information on a successful means used in wool sensitive patients who are compelled to remain in the industry has been found.

## FELIX VI SERUM FOR TYPHOID

*To the Editor:* The phrase "Felix Vi serum against typhoid" has come to my attention. Any information you can give me on this item will be appreciated. D. Paul Ward, M.D., Fort Ontario, N. Y.

ANSWER.—Felix believes that one of the important components of the typhoid organism is the Vi (virulence) antigen. He has prepared an antiserum rich in Vi antibodies which he suggests for therapeutic and prophylactic application.

So far as known this serum is not commercially available in this country and is still in the experimental stage.

## ZINC OXIDE INTRARECTALLY

*To the Editor:*—Can there be any deleterious results from using official zinc oxide intrarectally daily for chronic proctitis? M.D., Illinois.

ANSWER.—In considering any possible deleterious effects from the daily use of zinc oxide intrarectally, the local and possible systemic effect must be considered. Owing to its insolubility under the conditions mentioned, the degree of absorption of zinc oxide is practically nil. There is little likelihood of systemic or harmful local effects when zinc oxide is used for its soothing and protective action.

# Medical Examinations and Licensure

## COMING EXAMINATIONS

### NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: Parts I and II. Medical centers having five or more candidates desiring to take the examination, Feb. 12-14. Exec. Sec., Mr. Everett S. Elwood, 225 S. 15th St., Philadelphia.

### SPECIAL BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: An Affiliate of the American Board of Surgery. *Written.* Part I. Various places throughout the United States and Canada, March 28. *Oral.* Part II. New York, June 10-11. Applications must be received 60 days prior to examination. Sec., Dr. Paul M. Wood, 745 Fifth Ave., New York.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: November 1940. *If a sufficient number of applications are received before March 1, there will be an examination at New York, June 10-14.* Sec., Dr. C. Guy Lane, Marlboro St., Boston.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Various sections of the United States, Feb. 19. Formal application must be received on or before Jan. 1. Sec., Dr. William S. Middleton, 1301 University Ave., Madison, Wis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *General oral and pathologic examinations (Part II) for all candidates (Groups A and B)* will be conducted in Atlantic City, N. J., June 8-11. *Applications for admission to Group A, Part II examinations must be on file not later than March 15.* Sec., Dr. Paul Titus, 1015 Highland Bldg., Pittsburgh (6).

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* Various cities of the United States and Canada, March 2. (The only written examination in 1940.) Oral. New York, June 8-10. *Formal applications must be received before Jan. 1.* Sec., Dr. John Green, 6830 Waterman Ave., St. Louis.

AMERICAN BOARD OF OTOLARYNGOLOGY: New York, June 3-5. Sec., Dr. W. P. Wherry, 1500 Medical Arts Bldg., Omaha.

AMERICAN BOARD OF PATHOLOGY: New York, June 10-11. Sec., Dr. F. W. Hartman, Henry Ford Hospital, Detroit.

AMERICAN BOARD OF PEDIATRICS: New York, April 30 and May 1. Kansas City, Mo., preceding the Region III meeting of the American Academy of Pediatrics, Seattle, June 2. Sec., Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York, Dec. 18-19. Sec., Dr. Walter Freeman, 1028 Connecticut Ave. N.W., Washington D. C.

## California July Examination

Dr. Charles B. Pinkham, secretary, California State Board of Medical Examiners, reports the written examination held at San Francisco, July 11-13, 1939. The examination covered nine subjects and included 90 questions. An average of 75 per cent was required to pass. Two hundred and fifteen candidates were examined, 204 of whom passed and eleven failed. The following schools were represented:

| School | PASSED | Year Grad. | Per Cent |
|---|---|---|---|
| College of Medical Evangelists | | (1938) | 83.2, 85.8, (1939) 75.1, 75.9, 75.9, 76, 76.1, 78.8, 79.2, 79.7, 79.7, 79.8, 81.1, 81.2, 81.8, 82.4, 82.9, 82.9, 83.3, 83.8, 84.6, 84.8, 84.8, 85, 85.1, 85.8, 85.9, 87.3, 88.7 |
| Stanford University School of Medicine | | (1938) | 84.1, (1939) 76.3, 77.8, 78.1, 78.4, 79.1, 79.2, 79.8, 79.9, 80.1, 80.6, 81.2, 81.7, 82, 82, 82.2, 82.4, 82.6, 82.6, 82.7, 82.8, 83.1, 83.1, 83.3, 83.3, 83.3, 83.7, 83.9, 84.6, 85, 85.4, 85.8, 85.8, 85.8, 86, 86.1, 87.1, 87.2, 87.8, 87.8, 88, 89.7, 89.8 |
| University of California Medical School | | (1938) | 85.6, 87, (1939) 75.1, 76.3, 78, 78.3, 80.6, 80.6, 80.7, 80.7, 81, 81, 81.1, 81.1, 81.3, 81.4, 81.8, 82.3, 82.3, 82.4, 82.4, 82.6, 82.6, 82.6, 82.6, 83.4, 83.6, 83.6, 83.6, 83.7, 83.8, 83.9, 83.9, 84.1, 84.3, 84.3, 84.6, 85, 85, 85, 85.3, 85.4, 85.7, 86.3, 86.6, 86.6, 86.7, 87, 87.1, 87.3 |
| University of Southern California School of Medicine | (1939) | | 77.9, 78.1, 78.8, 81, 81.1, 81.1, 81.2, 81.7, 82, 83, 83.2, 83.4, 84, 84, 84.1, 84.2, 84.8, 86.4, 86.8, 87.7 |
| University of Colorado School of Medicine | | (1938) | 82.8 |
| Northwestern University Medical School | | (1938) | 82, (1939) 82.8, 82.3 |
| Rush Medical College | | (1937) | 84.8* |
| University of Illinois College of Medicine | | (1938) | 81.3, (1939) 80.3, 81 |
| Indiana University School of Medicine | | (1938) | 79.3 |
| State University of Iowa College of Medicine | | (1938) | 78, 81.6, (1939) 77.9, 83.8 |
| University of Kansas School of Medicine | | (1938) | 80.6 |
| University of Louisville School of Medicine | | (1938) | 76.6 |
| Louisiana State University School of Medicine | | (1939) | 90.3 |
| Johns Hopkins University School of Medicine | | (1936) | 83 |
| Harvard Medical School | | (1938) | 83.2, (1939) 80.6 |
| University of Minnesota Medical School | | (1939) | 82.6 |
| Washington Univ. School of Medicine | | (1938) | 77, 82.3, (1939) 79.2 |
| Creighton University School of Medicine | | (1938) | 75.2, 76, 80.8, (1939) 79.7, 85.1, 85.4 |
| University of Nebraska College of Medicine | | (1938) | 77.8, 80.9 |
| Albany Medical College | | (1938) | 88.3 |
| Columbia University College of Physicians and Surgeons | (1937) | | 83.1, (1939) 80.4 |
| University of Oklahoma School of Medicine | (1938) | | 81.4, (1939) 79.9 |
| University of Oregon Medical School | | (1938) | 79.2, 81.4, 82.6, 83.4, 86.2, (1939) 83.1 |
| Jefferson Medical College of Philadelphia | | (1938) | 76.7, 86.9 |
| University of Pennsylvania School of Medicine | | (1938) | 82.4 |
| Marquette University School of Medicine | | (1939) | 79.3, 79.3 |
| University of Wisconsin Medical School | | (1938) | 84 |
| McGill University Faculty of Medicine | | (1938) | 77.4, 78.2, 79.1, 80.6, 85.4, 87 |
| Medizinische Fakultät der Universität Wien | | (1924) | 80.2 |
| Licentiate of the Royal College of Physicians of London and Member of the Royal College of Physicians and Surgeons of England | | (1938) | 85.2 |
| Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg | | (1919) | 75.7 |
| Friedrich-Alexanders-Universität Medizinische Fakultät, Erlangen | | (1923) | 88 |
| Johann Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt-am-Main | | (1922) | 86.7 |
| Ludwig-Maximilians-Universität Medizinische Fakultät, München | | (1926) | 84 |
| University of Edinburgh Faculty of Medicine | | (1925) | 84 |
| Second Moscow Medical Institute | | (1926) | 83.3 |

| School | FAILED | Year Grad. | Per Cent |
|---|---|---|---|
| College of Medical Evangelists | | (1939) | 74.6 |
| Stanford University School of Medicine | | (1936) 69.7, (1939) | 70.6 |
| University of California Medical School | | (1939) | 71.2 |
| Rush Medical College | | (1938) 72.8, | 74.1 |
| University of Minnesota Medical School | | (1939) | 74.8 |
| Creighton University School of Medicine | | (1939) 72.7, | 72.8 |
| Marquette University School of Medicine | | (1938) | 71.3 |
| Universität Heidelberg Medizinische Fakultät | | (1915) | 67.4 |

Ninty-nine physicians were licensed by reciprocity and nineteen physicians were licensed by endorsement from March 24 through September 11. The following schools were represented:

| School | LICENSED BY RECIPROCITY | Year Grad. | Reciprocity with |
|---|---|---|---|
| University of Arkansas School of Medicine | | (1925) | Nebraska, (1938, 2) Arkansas |
| College of Medical Evangelists | | (1934) | Colorado |
| Stanford University School of Medicine | | (1929) | Illinois |
| University of Colorado School of Medicine | | (1933) | Colorado |
| George Washington University School of Medicine | | (1934) | New York |
| Jenner Medical College | | (1911) | Illinois |
| Northwestern University Medical School | | (1933) | Illinois |
| Rush Medical College | (1894), (1928) | Illinois, (1935) | Ohio |
| University of Illinois College of Medicine | | (1930), (1935) | Illinois |
| Indiana University School of Medicine | | (1926), (1932) | Indiana |
| State University of Iowa College of Medicine | | (1924), (1928), (1932), (1933, 2) | Iowa |
| University of Kansas School of Medicine | | (1929), (1931), (1936), (1937) | Kansas |
| University of Louisville School of Medicine | | (1932) | Missouri |
| Tulane University of Louisiana School of Medicine | | (1934), (1937), (1938) | Louisiana |
| Johns Hopkins University School of Medicine | | (1931), (1935) | Maryland |
| Harvard Medical School | | (1937) | New York |
| University of Michigan Medical School | | (1921) | R. Island, (1928), (1934), (1935) Michigan |
| Detroit College of Medicine and Surgery | | (1929), (1930) | Michigan |
| University of Minnesota Medical School | | (1929) | Montana |
| Barnes Medical College | | (1907) | Illinois |
| St. Louis College of Physicians and Surgeons | | (1914) | Missouri |
| University Medical College of Kansas City | | (1908) | Kansas |
| Washington University School of Medicine | | (1928) | Illinois, (1896), (1925), (1936), (1937) Missouri |
| Creighton University School of Medicine | | (1928) | Kansas, (1926), (1927), (1938, 3) Nebraska |
| University of Nebraska College of Medicine | | (1925) | Arizona, (1926) Montana, (1925), (1935, 2), (1937), (1938, 2) Nebraska |
| Columbia Univ. College of Physicians and Surgeons | | (1936, 2) | New York |
| Cornell University Medical College | | (1926) | New York |
| Long Island College of Medicine | | (1926), (1936) | Kentucky |
| New York Homeopathic Medical College and Flower Hospital | | (1931), (1935) | New York |
| New York University College of Medicine | | (1935) | New York |
| University and Bellevue Hospital Medical College | | (1912), (1918), (1921) | New York |
| University of Rochester School of Medicine | | (1936) | New York |
| Eclectic Medical College, Cincinnati | | (1925) | Ohio |
| Western Reserve University School of Medicine | | (1935) | Ohio |
| University of Oregon Medical School | | (1919), (1931) | New York, (1930) Washington, (1931), (1935), (1936, 2) Oregon |
| Hahnemann Med. College and Hospital of Philadelphia | | (1900) | New Jersey |
| Jefferson Medical College of Philadelphia | | (1921) | Penna. |
| University of Pennsylvania School of Medicine | | (1933) | Penna., (1934) Minnesota, (1936) New York |
| Western Pennsylvania Medical College | | (1906) | Penna. |
| Medical College of the State of South Carolina | | (1935) | S. Carolina |
| Meharry Medical College | | (1927) | N. Carolina |
| University of Tennessee College of Medicine | | (1928) | Tennessee |
| Baylor University College of Medicine | | (1935) | Texas |
| University of Texas School of Medicine | | (1927), (1936) | Texas |
| Marquette University School of Medicine | | (1937) | Wisconsin |
| University of Wisconsin Medical School | | (1932) | Wisconsin |
| Trinity Medical College | | (1896) | Illinois |
| Universität Zürich Medizinische Fakultät | | (1926) | New York |

| School | LICENSED BY ENDORSEMENT | Year Grad. | Endorsement of |
|---|---|---|---|
| College of Medical Evangelists | | (1930), (1937) | N. B. M. Ex. |
| University of California Medical School | | (1937) | N. B. M. Ex. |
| University of Southern California School of Medicine | | (1939) | U. S. Navy |
| University of Colorado School of Medicine | | (1929) | U. S. Navy |
| Yale University School of Medicine | | (1933) | N. B. M. Ex. |
| George Washington University School of Medicine | | (1937) | N. B. M. Ex. |
| Chicago College of Medicine and Surgery | | (1917) | U. S. Army |
| Boston University School of Medicine | | (1932) | N. B. M. Ex. |
| Harvard Medical School | | (1934), (1935) | N. B. M. Ex. |
| University of Michigan Medical School | | (1917) | U. S. Navy |
| University of Minnesota Medical School | | (1938) | U. S. Navy |
| Washington University School of Medicine | | (1936) | N. B. M. Ex. |
| New York Medical College and Flower Hospital | | (1936) | N. B. M. Ex. |
| University of Oregon Medical School | | (1933) | Alaska, N. B. M. Ex. |
| Vanderbilt University School of Medicine | | (1931) | U. S. Navy |
| Medical College of Virginia | | (1918) | U. S. Navy |
| University of Wisconsin Medical School | | (1933) | N. B. M. Ex. |

# Book Notices

**Public Health Law.** By James A. Tobey, Dr.P.H., LL.D., Lecturer on Public Health Law at Harvard University School of Public Health, Boston. Second edition. Cloth. Price, $3.50. Pp. 414. New York: Commonwealth Fund; London: Oxford University Press, 1939.

This edition of Public Health Law is much more comprehensive than the author's earlier volume and has been completely rewritten. The volume is a modern textbook on the important phases of the laws of public health. The publication, therefore, should find importance to those concerned in the various phases of public health and its administration. The text is divided into four major portions, on public health law and administration, the powers and duties of health departments, liability, which includes a thorough discussion of personal liability of health officers, and legislation and law enforcement. Under these four major headings, public health law is discussed in a simple and interesting manner. At the same time there is very little personal opinion of the author. The text is based on facts and references to higher court decisions. Because of the importance of a thorough knowledge of public health law and all its phases to health officers, students of public health, physicians, judges, attorneys, government officials and others, a selected bibliography on public health administration and legal aspects of public health has been gathered by Dr. Tobey. Occasionally public health officials who have been attempting to discharge their duties conscientiously and impartially are distressed to find themselves confronted with indictment or injunction proceedings. Defenses against these legal actions not only are time consuming but may interfere with the proper conduct of official duties and are often unnecessarily expensive. It is highly important, therefore, that health officials discharge their duties with the minimum of litigation either by or against them. Of course there are occasions when court action is necessary as a last resort. For such occasions the wise health official will be amply prepared not only by his conduct but by his familiarity with legal principles applicable to public health. This book may help him attain such familiarity.

**The Principles of Dental Medicine: The Medical Aspects of Dental Disease.** By F. W. Broderick, M.R.C.S., L.R.C.P., L.D.S., Hon. Dental Physician to the Royal Victoria and West Hants Hospital, London. Third edition. Cloth. Price, $7.50. Pp. 575, with 44 illustrations. St. Louis: C. V. Mosby Company, 1939.

> A fool is bent upon a twig, but wise men dread a bandit.
> Which I think must have been clever, for I didn't understand it.

This quotation, taken from the review (*Bristol M.-Chir. J.* **53**:114 (summer) 1936) of the Common Cold and Influenza by J. E. R. McDonagh, may with equal aptitude be applied to Broderick's book. The latter has based his text largely on the theories and terminology of McDonagh, both of which are so unusual that the reader has to acquire not only new definitions for words commonly used by physicians, physiologists and biochemists but also an entirely new theory for the mechanism of disease. No doubt most of those who read it will label it "clever," though probably because they don't "understand it." The arrangement is faulty, there is a great deal of repetition, and quotations from other authors are overnumerous and many inept. McDonagh and Broderick's notions are summed up in the latter's statement "Disease being, as we have seen, primarily the consequence of the condensation of one protein particle by another, in the process of which the less condensed is robbed of electrons by the more condensed, it depends essentially on the existence of a state of colloidal disequilibrium." Dental caries, Broderick believes, is due to pure dehydration (acidosis, agglutination) of the colloidal protein particles of the blood plasma and pyorrhea to pure hydration (alkalosis, dispersion). It should be noted that he uses such terms as hydration and dispersion in special senses quite different from conventional practice. Gingivitis is the result of colloidal disequilibrium between dehydration and hydration and a connecting link between pyorrhea and caries. The extreme degree to which such ideas have been carried by him is illustrated by the following: "Another factor which needs mention is that of masturbation, a circumstance which may definitely play a part in the production of dental caries through metabolic upset in the direction of an acidosis." The book is divided into three parts: part I, general physiologic considerations, treats of such subjects as acid-base balance, vegetative nervous system, endocrine system, colloidal state, calcium metabolism, saliva, nature and cause of disease; part II, dental medicine, including etiology and prevention of caries and pyorrhea, action of drugs, aim of medical treatment, experimental methods; part III, relation of dental to general medicine, covering effect of civilization, effect of dental sepsis, teeth in arthritis, allergic disease, tuberculosis, malignant disease, diabetes and pregnancy. The formal text is concluded by the introduction of twenty-five case histories illustrating the author's methods of diagnosis and treatment.

**Le cancer de l'estomac au début: Étude clinique, radiologique et anatomo-pathologique.** Par René-A. Gutmann, médecin des hôpitaux de Paris, Ivan Bertrand, directeur à l'École des Hautes Études, et Th. J. Péristiany, assistant à la consultation de gastro-entérologie de la Salpêtrière. Préface du Pr A. Gosset. Cloth. Price, 360 francs. Pp. 493, with 563 illustrations. Paris: G. Doin & Cie, 1939.

There is an introduction by Prof. Antonin Gosset. This publication is the only one of its kind dealing exclusively and extensively with gastric cancer in its earliest stages. The appearance of such a work is extremely welcome not only because of the importance of the subject matter but because of the enviable reputation of the senior author, an experienced and skilful gastro-enterologist. For serious students of the clinical and radiologic aspects of gastric disease an English translation is highly desirable. The subject matter is arranged in the following order: clinical 111 pages, radiologic 170 pages, methods of laboratory examination thirty pages, treatment ten pages, and gross and microscopic pathology 150 pages.

Gutmann and his collaborators emphasize the important fact that any gastric disorder of recent onset which is of a persistent nature and recurs should be considered as serious until proved otherwise. They describe three clinical types of gastric carcinoma: latent, painless and painful. Clinicians will heartily approve the strong emphasis placed on the observation that the symptoms and signs of early carcinoma are often lacking, trivial or distorted. Included in the first type are patients with a symptomless epigastric tumor or with such initial symptoms as edema or those engendered by metastases. The second type may be characterized by nothing but a vague indigestion, which may at the outset be temporarily relieved by treatment, or by such symptoms as anorexia, nausea, vomiting, dysphagia, aerophagia, hemorrhage, hunger pain, constipation, diarrhea, fever or loss of weight or strength, any one of which, or a combination of which, may be the initial and exclusive complaint. The painful form has its origin in ulcer-like cancer (le cancer ulcériforme), cancer on ulcer (l'ulcère transformé) and a third form designated le cancer gastrique muco-érosif à marche lente. This is a rare superficial variety with ulcer-like symptoms of long duration, not of progressive severity, which may remain localized to the mucosa for a long period. The aforementioned three types are illustrated by short case histories.

The authors have also had the experience that malignant ulcers may appear to heal, or be temporarily healed, under medical treatment. To show how frequently one sees early ulcer-like lesions, Gutmann and his co-workers (page 52) state that during the last 300 gastrectomies performed in their clinic there were removed eighty-five ordinary vegetative cancers, 133 benign ulcers, forty-three ulcers which had apparently begun benignly and then later became malignant, and thirty-nine ulcer-like cancers.

From a roentgenologic standpoint early gastric cancer consists of three general forms: infiltrating, ulcerating and tumefactive (formes végétantes). The former is characterized by the presence of localized regions of rigidity, by cone shaped or pencil point defects of the pylorus, by "aspect encastré" or by undulating or lacunar forms of filling defects. The ulcerating form is characterized in order of importance by the niche en plateau, an elevated defect in contrast to the depressed or dish-like image encastrée, by the large triangular niche, by the niche encastrée, and by the meniscus sign (la niche à ménisque). Contrary to what is generally believed, the authors think that the last mentioned sign is not pathognomonic for cancer and that it should be interpreted with caution because, in their opinion, this sign may be produced by periulcerous inflammatory changes. One procedure which appears logical to the clinician, and which should be employed more often by the radiologist, is the routine

treatment of these patients for from four to six weeks and reexamination thereafter. The effect of such treatment often appears decisive in arriving at a final diagnosis in these early lesions.

In the authors' opinion it is not possible to make a diagnosis of incipient carcinoma by the gastroscope; gastric analysis is of no help in the diagnosis of early cancer; though decidedly inferior to roentgenologic examination, the systematic examination of the feces for occult blood is more important than the other methods; serologic and cytologic studies are of no value in the diagnosis of early cancer; the classic chronic gastritis is not considered the precursor of cancer, although there may be a gastritic stage of incipient cancer; there appears to be no justification for gastric resection for gastritis in order to avoid gastric cancer.

The section on gross and microscopic anatomy of the disease is highly instructive and convincing, and the illustrations are numerous, ample and clear. As a matter of fact, the illustrations throughout the book are all that one could desire.

To many roentgenologists the section on roentgenologic diagnosis may prove disappointing, chiefly because the value of roentgenoscopy, study of the mucosal relief and the significance of the meniscus sign are belittled. On the contrary, a study of the barium-filled stomach is extolled. Granting that the authors' method of examination and interpretation may result in early diagnosis of early cancer in a large proportion of cases, many able roentgenologists maintain that roentgenoscopy will reveal early gastric cancer with a high degree of accuracy, that inspection of the internal relief is highly informative and frequently indispensable, and that the meniscus complex, properly determined, is consistently indicative of ulcerating carcinoma. Apparently the authors are not familiar with, or they do not endorse, the quick staining method of frozen sections, which was developed in this country. Their attitude on gastritis as a precursor to cancer, and on gastroscopic diagnosis, will undoubtedly be challenged in many quarters. Only a few of the important American contributions to the subject of gastric cancer masquerading as benign gastric ulcer are cited.

**Traité d'ophtalmologie.** Publié sous les auspices de la Société française d'ophtalmologie. Par MM. P. Bailliart, Ch. Coutela, E. Redslob, E. Velter. René Onfray: Secrétaire général. Tome IV: Pathologie (suite). Par MM. A. Cuénod et al. Cloth. Price, 400 francs. Pp. 890, with illustrations. Paris: Masson & Cie, 1939.

The fourth volume of this new French encyclopedia follows the general form of its predecessors and is given over to the pathologic conditions of the anterior portions of the eye. The text consists of the pathology of the lacrimal apparatus by Vallière-Vialeix of Limoges, diseases of the conjunctiva by Renard of Paris and Nataf of Tunis, trachoma by Cuénod and Nataf of Tunis, conjunctival lesions resulting from systemic disorders and exanthems by Genet of Lyons, conjunctival lesions produced by chemical substances or by products of animal or vegetable origin by Genet, conjunctival lesions produced by physical agents by Genet, new formations and tumors of the conjunctiva by Merigot de Treigny of Paris, diseases of the cornea by Prélat of Paris, diverse disorders of the cornea by Kleefeld of Brussels, and diseases of the sclera by Petit of Paris. Naturally with such a variety of authors there is a wide variation in the character of the individual chapters. The first 300 pages of the book is devoted to diseases of the entire lacrimal apparatus and nowhere in the literature is there such a careful systematic compilation as this. That chapter is profusely illustrated by reproductions of photographs, mostly black and white. The pictures of the external face are good, the reproductions of roentgenograms of the tear passages are rather indifferent, and the photomicrographs of the pathologic changes are excellent. The remainder of the book is extensively illustrated with color plates, some reproductions of drawings and some color photographs. On the whole these are excellent, particularly those showing biomicroscopic aspects. Unfortunately, the chapter dealing with the cornea contains comparatively few and rather indifferent illustrations. Particularly appropriate at this time is an eight page section that starts with the following short paragraph: "The appearance of the ocular manifestations due to yperite date from the end of July 1917. At that period the British front in the Ypres sector was subjected to a bombardment by poisonous substances which were up to that time unknown and which produced the ocular disturbances that we are about to describe. Hence the name 'yperite.'" Then follows a careful description of the inflammation of the eyes caused by yperite, or mustard gas, together with treatment and prognosis. To the American ophthalmologists who were not at the front, this condition is practically unknown. By and large, volume IV is up to the standard set for the entire encyclopedia. In some ways, particularly color reproductions, it surpasses its predecessors, while in some chapters the text matter is not as complete as could be wished for in a work of this extent. However, it is so good that it is to be devoutly hoped that the war will not interfere with the completion of the series.

**Medical Climatology: Climatic and Weather Influences in Health and Disease.** By Clarence A. Mills, Ph.D., M.D., Professor of Experimental Medicine, University of Cincinnati, Cincinnati. Cloth. Price, $4.50. Pp. 296, with 90 illustrations. Springfield, Illinois, & Baltimore: Charles C. Thomas, 1939.

Chapter I opens by differentiating sharply between weather and climate. By weather in a meteorologic sense is meant the sum total of atmospheric conditions prevailing from hour to hour and from day to day or week to week. Climate, however, refers to average conditions over many years or decades and while more stable than weather should not be thought of as a fixed term to cover unchanging values. This book deals definitely with variations in climate; i. e., different climatic areas rather than with weather as defined. Climate, Mills says, plays a distinct part in average body heat loss and energy output, therefore exerting a preponderant role in the existence of man and other warm blooded animals. There is a climatic dominance of growth, fertility, metabolism, body resistance, vascular system and other human functions. Mills has not attempted in this book to cite the mass of evidence for the role of climate in so many functions and human diseases. In spite of the author's statement in the preface that he does not desire to hold climate and weather responsible for all human reactions, the reading of the book demands the constant exercise of the critical faculties to avoid this conclusion. Pitfalls are numerous and many readers will have difficulty in grasping such statements as this made on page 184: "World leaders listed in Who's Who and other similar volumes, and the presidents of the United States, have largely been born in the more stimulating and unstable first half of each year. The feebleminded, on the other hand, are more often conceived in summer or early fall, when fewer superior minded individuals are being conceived. And in the matter of admission to mental hospitals, this same relationship to seasonal stress is found." Many statements perhaps equally difficult to confirm are made in other portions of the book but may not be quite so obvious.

**Opuscula selecta Neerlandicorum de arte medica.** Fasciculus quintusdecimus quem curatores miscellaneorum quae vocantur Nederlandsch Tijdschrift voor Geneeskunde collegerunt et ediderunt Amstelodami Sumptibus Societatis. Petri Camperi itinera in Angliam 1748-1785. [Selected Dutch Writings on Medical Art. No. 15. Travels of Petrus Camper in England 1748-1785.] Cloth. Pp. 264, with illustrations. Amsterdam, [n. d.].

This volume of the remarkable series issued by the *Nederlandsch tijdschrift voor geneeskunde* contains the diaries of Petrus Camper, "the most famous Dutch doctor of the second half of the eighteenth century," during his visits to England in 1748-1749, 1752 and again in 1785. B. W. T. Nuyens writes an interesting introduction and critical review of the diaries. The diaries are in the Dutch language, with translation into English on the opposite pages. The diary of the first visit to London is accompanied by "annotations to a course of lectures on midwifery delivered by the wellknown Doctor W. Smellie" in Latin with English translation and illustrated by facsimile reproductions of the title page of the summary of Smellie's course and of the first two pages of Camper's annotations. The diaries record in detail Camper's daily experiences during his English visits. "When in 1748 as a young doctor, in 1752 as a youthful professor at Franeker's university, he [Camper] went to England he did this to improve his skill in the medical science, preferably in midwifery. When, thirty-seven years later, in 1785 he revisited England, he went as a scientific man of mature experience, to communicate to his English colleagues his

self-assured ideas on obstetrics, the fruits of . . . a long practice." During his second visit William Hunter invited him to dinner, of which he writes: "Had dinner at Hunter's on Wednesday (19th July) and saw his drawings of the uterus gravidus, which were very finely drawn by Rymsdyk." There are seventeen illustrations which show portraits of Camper, several drawings by him, and also a portrait of Smellie by himself. At the end are biographic notes of persons mentioned in the diaries. Readers of medical history, and especially those concerned with obstetric history, will find this book of exceptional interest.

**Traffic in Opium and Other Dangerous Drugs for the Year Ended December 31, 1938.** Report by the Government of the United States of America. U. S. Treasury Department, Bureau of Narcotics. Cloth. Price, 20 cents. Pp. 122, with illustrations. Washington, D. C.: Supt. of Doc., Government Printing Office, 1939.

This report by the Commissioner of Narcotics to the Secretary of the Treasury deals with the calendar year ended Dec. 31, 1938. It indicates that there are still seven states which have not passed the uniform narcotic drug act; namely, Kansas, Maine, Massachusetts, New Hampshire, Washington, North Dakota and Vermont. The control of drug addiction in the United States continues to be satisfactory. Apparently the number of drug addicts has decreased from ten per 10,000 persons in 1924 to two per 10,000 persons at the present time. The treatment used in the government hospitals includes withdrawal of the drugs within fourteen days, warm baths, sedatives when necessary, and supplementary measures as indicated. A recent survey indicates that three years after the date of discharge 34 per cent have not relapsed. Research is being conducted as to non-habit forming drugs which may be used to replace opium. Studies are also being made on narcotic addiction and crime. In the section of the book devoted to traffic in opium there are some interesting stories dealing with illicit traffic in narcotic drugs, each of them dramatic and each of them indicating the difficulty in controlling illicit traffic in opium. The records fortunately report but few instances in which physicians have been conspicuously mixed with this traffic. The per capita consumption of opium in the form of all its salts, derivatives and preparations amounted to approximately 7.4 grains for 1938. The per capita consumption of cocaine alkaloid was approximately 0.09 grain.

**The History of the Forceps: An Investigation on the Occurrence, Evolution and Use of the Forceps from Prehistoric Times to the Present Day.** By Vilhelm Møller-Christensen. (With a Summary in Danish). Denne Afhandling er af det lægevidenskabelige Fakultet antaget for den medicinske Doktorgrad, København. Translated from the Danish by W. E. Calvert. Paper. Pp. 298, with 441 illustrations. Copenhagen: Levin & Munksgaard; London: Oxford University Press, 1938.

In 1931 the author devised a three legged suture forceps and before publishing a description of it he reviewed various German, British and French instrument catalogues to make certain that his invention was original. He was amazed to find that in one catalogue (Jetter and Scheerer's Aesculap Musterbuch) there were more than a thousand different forceps. Of course, many of the models differed only slightly but there were at least 200 different types. The author then undertook to study the sources from which this "world of forceps" arose. For this purpose he reviewed not only medico-historical but also archeological literature. Furthermore, he visited many museums both in his native country (Denmark) and abroad (Sweden, France, Italy, Great Britain and Germany). Illustrations were made of a large number of different types of forceps and in this book the author has included 441 of them. The author defines forceps as a gripping instrument which consists of two legs joined together in a hoop, or forged solidly together or emanating from a solid metal rod and terminating at the other end in the gripping parts, the jaws. The author points out that the original model of the forceps was the hand, when its thumb and index finger are used for gripping. When the hand, used as a forceps, grips coarse objects the finger pulpae act as the jaws, whereas when gripping finer objects it is the nails that act as the forceps jaws. The book is extremely interesting and abundantly illustrated. It represents an enormous amount of hard work and considerable travel, and the author is to be congratulated on his accomplishment.

**Diseases of the Mouth and Their Treatment: A Text-Book for Practitioners and Students of Medicine and Dentistry.** By Hermann Prinz, A.M., D.D.S., M.D., and Sigmund S. Greenbaum, B.S., M.D., F.A.C.P., Professor of Clinical Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Second edition. Cloth. Price, $9. Pp. 670, with 336 illustrations. Philadelphia: Lea & Febiger, 1939.

This is a collection and evaluation of important contributions concerning the diseases of the mouth and their treatment, the second edition of a work designed as a textbook for students and practitioners of medicine and dentistry. In this edition the book has been thoroughly revised and a new chapter on lymphadenitis has been added together with articles on Paget's disease (osteitis deformans), Schüller-Christian disease, hereditary pseudohemophilia, sarcoidosis and many other conditions productive of mouth lesions. In addition there are articles on microscopic technic, roentgenographic examination, mouth breathing, harelip and cleft palate, and diseases of the mouth associated with nervous disorders. There is also a complete classification of tumors of the mouth. Seventy-five illustrations have been added and many of the older ones have been replaced. Since this book is intended as a textbook rather than a reference work, some of the subjects of lesser importance are given only a little space. Those of importance are handled adequately. Nothing of importance has been omitted, and though the book is of only medium size it is an adequate discussion of the common diseases of the mouth and of every disease productive of mouth lesions. The text is well written, the illustrations are for the most part excellent. The type is large and legible. It should satisfy a need long felt by dermatologists, oral surgeons and the general practitioner.

**Die Pflege des gesunden und kranken Kindes: Zugleich ein Lehrbuch der Ausbildung zur Säuglingspflegerin und Kinderkrankenschwester.** Unter Mitarbeit von R. Büttner et al. Herausgegeben von Prof. Dr. med. Werner Catel, Direktor der Universitäts-Kinderklinik und -Poliklinik, Leipzig. Paper. Price, 18 marks. Pp. 764, with 423 illustrations. Leipzig: Georg Thieme, 1939.

This is the longest textbook for nurses and nursemaids that has ever been written. One wonders whether a volume of 764 large pages will ever be read by nurses or nursemaids. The section on anatomy and physiology is excellent and would do justice to a special treatise on the anatomy and physiology of childhood. The rest of the book is well written but not as well as the first section. The book is all inclusive. It not only covers the ordinary care of the healthy and the sick child but it includes also a section on public health, child education and psychology, child play, and a section on the health of the mother. Significant of the present day political trend is the inclusion of a section on race theory. The content in this section, however, is mainly biologic. Significant also is an illustration in the chapter on play showing miniature soldiers and cannons as toys for children. The illustrations in the section on anatomy are excellent. Most of the illustrations in the other chapters are too small and some of them are indistinct.

**Pathologie chirurgicale de la rate.** Par Pierre Goinard, chirurgien des hôpitaux d'Alger. Paper. Price, 55 francs. Pp. 174, with 15 illustrations. Paris: Masson & Cie, 1939.

This monograph is the sixth in a series concerned with various diagnostic procedures and pathologic conditions of the spleen. The present volume, although dedicated to the surgical pathology of the spleen, covers a much wider field and considers in some detail almost all the important disease conditions which may affect that organ. The author particularly emphasizes the necessity for the clinician and surgeon to cooperate closely before surgical intervention is recommended. Ptosis of the spleen and torsion of the splenic pedicle, contusions and ruptures, as well as wounds and herniation of the spleen, are carefully considered and in most cases splenectomy rather than some other conservative operation is indicated. Splenomegaly due to various types of infections receives detailed mention, the chapter on hydatid cysts of the spleen being particularly valuable. The last half of the monograph is devoted to a consideration of the splenomegalies associated with pathologic blood conditions, changes in the liver and gastrointestinal hemorrhages, with a further chapter on Gaucher's and the Pick-Niemann disease. The author concludes that splenectomies are particularly valuable in hemolytic icterus and

are often indicated in other hemorrhagic conditions accompanied by splenomegaly. He discusses fully the relation of the spleen and splenectomy to so-called Banti's disease, emphasizing that, although the etiology of Banti's disease is not understood and that there are several conditions included under this term, nevertheless there are certain instances wherein splenic involvement either precedes or is not accompanied by cirrhosis of the liver, while in other instances the two are simultaneous in their development and in still other cases cirrhosis antedates involvement of the spleen. He does not see much value for splenectomy in this last group; in the first two, splenectomy may be of some benefit and occasionally cures. Statistics are quoted concerning the results of splenectomy under various circumstances and references to the literature are given. The technic of surgical procedures is carefully described. Illustrations of diseased spleens are almost entirely absent. The monograph as a whole gives a rather thorough review of the spleen from the surgical and diagnostic standpoint, but for a serious student of diseases of the spleen the treatment is rather superficial.

**Die infektiösen Krankheitsprozesse der Kniescheibe.** Von Sophus von Rosen. Acta orthopaedica Scandinavica, Supplementum III. Paper. Pp. 160, with 163 illustrations. Copenhagen: Einar Munksgaard, 1939.

In this monograph the author first presents an extensive review of the literature on tuberculosis and osteomyelitis of the patella. He then presents in detail a series of seven cases of tuberculosis and seven cases of osteomyelitis and compares his own observations with those of the authors in the preceding study. He feels that the prognosis in osteomyelitis is usually good as regards knee joint function, while in tuberculosis the result is most frequently ankylosis. In osteomyelitis simple drainage, usually with sequestrectomy, most often effects a cure, while in tuberculosis complete removal of the patella is recommended as the treatment of choice. From a critical analysis of the roentgenograms the author states that there is no characteristic roentgenologic difference between tuberculosis and osteomyelitis of the patella. He also points out that films of the normal growing patella may show numerous variations and irregularities and advises that in doubtful cases of patellar disease films should be made of the opposite patella for comparison. In the final chapter, von Rosen discusses those lesions of the patella recently described as Köhler's disease, or osteochondritis deformans juvenilis. He expresses his doubt that such a clinical entity exists and is of the opinion that the pathologic changes represent either a variation of the normal ossification picture or a benign osteomyelitis. This monograph should be of value to the general surgeon as well as to the orthopedist both for its excellent review of the literature and because of the original studies and logical conclusions of the author.

**Cardiovascular Diseases: Their Diagnosis and Treatment.** By David Scherf, M.D., Associate Professor of Clinical Medicine, The New York Medical College, New York, and Linn J. Boyd, M.D., F.A.C.P., Professor of Medicine, The New York Medical College. Cloth. Price, $6.25. Pp. 458. St. Louis: C. V. Mosby Company, 1939.

This book is based on a book previously published by the senior author, Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen, which has been extremely popular, having gone through four editions in four years. For the most part it is a literal translation of the German text with a considerable rearrangement of the various sections. A number of additions have been made, as for example that dealing with atelectasis, syphilitic myocardial involvement, the blood pressure in mitral diseases, the symptoms in tricuspid insufficiency, calcification of the aorta, pulmonary stenosis and regurgitation, the differentiation between rheumatic fever and subacute bacterial endocarditis, aneurysm of the aorta, vena cava thrombosis, periarteritis nodosa, painless coronary thrombosis and heart disease in the Negro. The sections on congenital heart disease and pericarditis have been completely reorganized and an attempt has been made to introduce American concepts of heart disease. It is hoped that in future editions the book will gradually shift to include more and more of the American point of view. Primarily this book serves to introduce the reader to the points of view which have been developed by the Viennese school, to which the senior author has contributed. It should be a welcome addition to the library of the internist and the general practitioner.

**Your Brain and Its Story.** By R. J. A. Berry, M.D., F.R.C.S., F.R.S.E., Director of Medical Services, Stoke Park Colony, Bristol. Cloth. Price, $2.50. Pp. 165, with 37 illustrations. New York, Toronto & London: Oxford University Press, 1939.

At the pressing request of the Gloucestershire Physiological Association, Professor Berry, anatomist, undertook to describe, for the public, the human brain as an instrument of the mind. With a sure hand the author leads the reader through the intricate maze of the phylogenic, structural and functional evolutions of the central and peripheral nervous systems. He continues by discussing craniometry and mental deficiency, and closes by portraying the social implications of his theme as a whole. Although the author presents many facets of his subject in the space of a few pages, the work is by no means slipshod or elementary. The volume bristles with unavoidable neuro-anatomic nomenclature but the terms are carefully defined and usefully employed. The illustrations are helpful and excellent. The intelligent and thoughtful reader will readily find the knowledge he seeks. Designed and intended for the public, the volume can be read with profit and appreciation by the medical student and physician, since it embodies what too many of the more technical works lack, namely the philosophy of the anatomist.

**The Infant and Child in Health and Disease with Special Reference to Nursing Care.** By John Zahorsky, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine, St. Louis, and Elizabeth Noyes, R.N., Supervisor and Instructor of Pediatrics, Children's Hospital, San Francisco, California. Second edition. Cloth. Price, $3. Pp. 496, with 140 illustrations. St. Louis: C. V. Mosby Company, 1939.

This book was published primarily for nurses specializing in the care of infants and children. It is practical, however, and may be found useful by others as well. The procedures presented are entirely modern and should meet with the approval of persons trained in the care of well and sick infants. The text covers much of the field of pediatrics, and practical nursing principles and technic are constantly stressed. The material is written in a simple and easily understandable style. The 140 illustrations are especially good. The third section of the book, devoted entirely to methods of procedure, should find especial usefulness for the nurse as well as the physician.

**Roentgen Technique.** By Clyde McNeill, M.D. Cloth. Price, $5. Pp. 315, with 268 illustrations. Springfield, Illinois, & Baltimore: Charles C. Thomas, 1939.

This book deals primarily with roentgen anatomy and positioning. Because of its simplicity and excellent illustrations it answers the need for a reliable book on the subject. The photographic reproductions of more than a hundred positions clearly record the relationship between the central ray and the organ to be roentgenographed or irradiated. Drawings taken from actual roentgenograms explain the anatomic features. The description of methods and technic is limited to a few precise sentences. Because of the constant advances in this field, only a small space is devoted to modern x-ray apparatus and exposures, thus rendering the book fairly independent of rapid changes. New methods, such as kymography and tomography, are however included. Charts and drawings on the epiphysial development and on accessory bones add practical value to the text. This surprisingly complete collection of anatomy and positioning, with the concisely arranged and excellent illustrative material, constitutes a valuable and practical volume for the roentgenologist, for those who are interested in teaching roentgen technic, and for the x-ray technician.

**Thérapeutique de la carie dentaire. II: Carie pénétrante: Traitement de la pulpe atteinte mais vivante (III^e^ degré de la carie).** Par le D^r^ G. Mahé. Paper. Price, 35 francs. Pp. 313, with 91 illustrations. Paris: The Author, [n. d.].

This volume is the second part of a treatise on the therapy of dental caries. The contents are presented in a clear and concise manner and are arranged essentially in the form of a series of lectures. Different types of carious teeth are classified according to the severity of the lesions present and their treatment is discussed. In addenda are included observations on such subjects as anesthetic preparations and amalgams. The book is amply supplied with diagrams and illustrations and contains a helpful indexed table of contents.

# Bureau of Legal Medicine and Legislation

## MEDICOLEGAL ABSTRACTS

**Life Insurance: "Sound Health" and "Serious Disease or Complaint" Construed.**—The defendant insurance company issued two life insurance policies which provided "If, . . . the insured . . . is not in sound health on the date hereof . . . or has, within two years before the date hereof, been attended by a physician for any serious disease or complaint . . . the Company may declare this policy void." On the death of the insured the defendant insurance company refused to pay the benefits stated in the policies, alleging that within the two years preceding the issuance of the policies the insured had been attended by a physician for high blood pressure, which the company claimed was a "serious disease or complaint." The plaintiff, the administratrix of the insured's estate, then brought suit. The trial court rendered judgment in favor of the plaintiff, but on appeal to the supreme court of New York, appellate division, fourth department, 252 App. Div. 926, 300 N. Y. S. 182, this judgment was reversed and the complaint dismissed. From the latter judgment the plaintiff appealed to the Court of Appeals of New York.

The evidence showed that the insured had suffered from high blood pressure, accompanied by dizzy spells, prior to her application for insurance, but there was also evidence that the insurer's agent knew of the insured's condition. A physician who attended her four months prior to the issuance of the policies testified that at intermittent periods she had a systolic blood pressure of between 190 and 200, but he did not testify either that she was suffering from a serious disease or complaint or that she was not in sound health. The evidence showed, too, that the insured, when she applied for insurance, was able to do her own housework and that the insurer's physician who examined her before the policies were issued reported that she was in good health.

Evidence could not properly be admitted, said the Court of Appeals, to show that the insured falsely stated in her application that she had not been under the care of a physician for three years, although in fact she had been attended by a physician within two years. Section 58 of the Insurance Law of New York requires that an insurance policy contain the entire contract and provides that nothing can be incorporated therein by reference. Consequently false statements, oral or written, made to induce an insurance company to issue a policy of insurance, even though they are material, do not constitute a defense unless they are attached to or endorsed on the policy. In the present case, the applications for insurance were neither attached to nor endorsed on those policies and so the statements in the applications were not warranties.

The burden of proof, said the Court of Appeals, rested on the insurer to justify its voiding its policies. It had to establish either that the insured had been attended by a physician for a serious disease or complaint within two years of the issuance of the policies or that she was not in sound health at the time the policies were issued. What constitutes a serious disease or sound health is ordinarily a matter of opinion. A condition which in one person might constitute a serious disease or complaint in another person might not be considered serious. The defendant, in the opinion of the court, failed to establish as a matter of law that the insured was not in sound health at the time the policies were issued or that she was suffering from a "serious disease or complaint."

There was evidence from which, the court thought, the jury could have found that the insurer's agent knew of the condition of the health of the insured. The court, however, was not in sympathy with the insurer's contention that because the agent had no authority to change the conditions of the policies the doctrine of equitable estoppel should not apply against it. Knowledge of the agent constituted knowledge on the part of the insurer. It would be a fraud on the policyholder to permit an insurer to accept premiums on a policy which it knew was void from its inception. Neither did the court look with favor on the insurer's contention that because the insured had not disclosed to the insurer's medical examiner the information that she had previously given to the insurer's agent, the insurer should not be estopped. The insured might well have believed that the medical examination had been required because of the information which she had given to the agent. Moreover, if the jury found, as apparently it did, that the insurer had not proved that the insured was not in sound health or had been attended by a physician within two years before the issuance of the policies for any "serious disease or complaint," the question of waiver or estoppel would be unimportant, and the trial court correctly so instructed.

The Court of Appeals ordered the judgment of the supreme court, appellate division, reversed and the judgment of the trial court in favor of the plaintiff affirmed.—*Lampke v. Metropolitan Life Ins. Co. (N. Y.), 18 N. E. (2d) 14.*

**Basic Science Acts: Application for Exemption Tardily Filed.**—The basic science act of Oklahoma, which became effective April 19, 1937, exempted from its requirements "Indian Herb Doctors, Herb Doctors or Doctors who administer simple remedies who register with this board [the basic science board] within sixty (60) days after the passage of this Act and who have practiced in Oklahoma for two (2) years." On June 18, 1937, the last day on which registration under the foregoing provision could be made, the defendant Adamson deposited in the United States mail at Oklahoma City an application, addressed to the secretary of the basic science examining board of Oklahoma, for exemption as a doctor who administered simple remedies. This letter was delivered June 21, 1937, or sixty-three days after the basic science act became effective. The board denied the application and Adamson instituted mandamus proceedings to compel the board to register him. The trial court granted the writ of mandamus on the theory, apparently, that the act of mailing the application was synonymous with the act of registering as required by the basic science act. The board thereupon appealed to the Supreme Court of Oklahoma.

In reversing the judgment of the trial court and remanding the cause, the Supreme Court said that where a person is required to register with a certain board within sixty days of a certain date in order to acquire a privilege under the law and he deposits his application in the United States mail on the sixtieth day, addressed to the secretary of the board more than 100 miles away, such act of mailing is not equivalent to registering, and if the application so mailed is not delivered until the sixty-third day it is too late. When a person elects to mail an application for registration, he thereby selects the United States mail as his agency, and the risk of delay in delivering is on him. The general rule, the court pointed out, is thus stated in 46 C. J. 559, sec. 69:

> In the absence of custom, statute, estoppel, or express contract stipulation, when a notice, affecting a right is sought to be served by mail, the service is not affected until the notice comes into the hands of the one to be served.

—*George et al. v. Adamson (Okla.), 86 P. (2d) 980.*

# Society Proceedings

## COMING MEETINGS

American Association for the Study of Neoplastic Diseases, Baltimore, Dec. 28-30. Dr. Eugene R. Whitmore, 2139 Wyoming Avenue N.W., Washington, D. C., Secretary.

Annual Congress on Industrial Health, Chicago, Jan. 15-16. Dr. C. M. Peterson, 535 North Dearborn St., Chicago, Secretary.

Eastern Section, American Laryngological, Rhinological and Otological Society, Pittsburgh, Jan. 5. Dr. John R. Simpson, Medical Arts Bldg., Pittsburgh, Chairman.

Middle Section, American Laryngological, Rhinological and Otological Society, Kansas City, Mo., Jan. 19. Dr. Sam E. Roberts, Professional Bldg., Kansas City, Mo., Chairman.

Society of American Bacteriologists, New Haven, Conn., Dec. 28-30. Dr. I. L. Baldwin, Agricultural Hall, University of Wisconsin, Madison, Wis., Secretary.

Southern Section, American Laryngological, Rhinological and Otological Society, Columbia, S. C., Jan. 8-9. Dr. Walter J. Bristow, Doctors Bldg., Columbia, S. C., Chairman.

Western Section, American Laryngological, Rhinological and Otological Society, Los Angeles, Jan. 26-27. Dr. Pierre Viole, 1930 Wilshire Blvd., Los Angeles, Chairman.

# Current Medical Literature

## AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1929 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but may be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

### Alabama State Medical Assn. Journal, Montgomery

**9:** 105-140 (Oct.) 1939

Changing Concepts of Deficiency Diseases. V. P. Sydenstricker, Augusta, Ga.—p. 105.
Use of Vitamins in Eye, Ear, Nose and Throat Practice. R. M. Clements and H. B. Searcy, Tuscaloosa.—p. 109.
Peptic Ulcer: Modern Conception of Surgical Treatment. M. Skinner, Selma.—p. 113.
Empyema Thorasis: Review of Progress in Treatment. J. M. Mason, Birmingham.—p. 116.
Obstetrics in Relation to Maternal Morbidity. J. Watson, Anniston.—p. 120.

### American J. Digestive Diseases, Huntington, Ind.

**6:** 505-588 (Oct.) 1939

*Clinical Significance of Carrier State in Amebiasis. J. T. Howard, Baltimore.—p. 505.
Perforation of Colon Complicating Bacillary Dysentery. D. N. Silverman, New Orleans.—p. 509.
Value of Peritoneoscopy in Gastro-Enterology: Review of 100 Cases. E. B. Benedict, Boston.—p. 512.
Discussion of Procedures Which Are Helpful in Diagnosing Lesions of Esophagus. H. E. Wright, Baltimore.—p. 519.
Gastritis Simulating Tumor Formation. R. Schindler, Chicago.—p. 523.
Characteristics of Normal Human Gastric Secretory Curve, Using Improved Gastric Test-Meal. C. M. Wilhelmj and A. Sachs, Omaha.—p. 529.
Absorption and Dilution of Glucose Solutions in Human Stomach and Duodenum. H. Shay, J. Gershon-Cohen, S. S. Fels and F. L. Munro, with technical assistance of H. Siplet, Philadelphia.—p. 535.
Test for Intestinal Absorption. T. L. Althausen, San Francisco.—p. 544.
Experimental Study of Effect of Thyroid on Motility of Gastrointestinal Tract. S. Morrison and M. Feldman, Baltimore.—p. 549.

**Carrier State in Amebiasis.**—Howard discusses the clinical state of twenty-two carriers of Endamoeba histolytica. These patients had abdominal complaints other than frank diarrhea or dysentery; they had no other intra-abdominal or extra-abdominal disorder. The symptoms in all were severe enough to make the patients consult their physicians or to make them go to a hospital dispensary. They were given routine gastrointestinal examinations, a complete physical examination, blood count, serologic test for syphilis, gastric analysis after an Ewald test meal, fluoroscopic examination after the administration of barium sulfate and proctoscopic examinations and stool studies. The preliminary diagnoses varied. The most common symptoms were pain, nervousness, gas with the passage of flatus, mucus in the stool, alternating constipation and diarrhea, and unformed stools or slight diarrhea. Each of the patients was given amebicidal therapy (emetine, carbarsone and/or chiniofon). Two patients required a second course of amebicidal therapy. There were no drug reactions. Fecal specimens passed without purgation and after purgation were examined at irregular intervals and no endamebas were found after treatment. At least three specimens were studied in each case three or more months after treatment had been completed. During treatment (which necessarily included relative rest and probably a little suggestion) and directly after treatment all but three patients were improved subjectively. The three who were not improved were neurotic, poorly adjusted women. Both patients who were not rid of their amebas by the first course of treatment said that they felt better after the ineffective therapy. Three months and longer after the eradication of amebas and with the stools still microscopically negative for Endamoeba histolytica, only six of the twenty-two carriers considered themselves to be strikingly better or to be digestively well as the result of treatment. The original symptoms in these six cases had caused them to be classified in the group of unstable colons at the time of the first examination. Nine of the fifteen carriers who continued to complain were given bromide or phenobarbital, a smooth diet, antispasmodics and directions for colon management. Seven of these were improved with this type of therapy when amebicidal treatment alone had failed to give real improvement. Amebiasis should be looked for in all patients with gastrointestinal complaints, but too striking clinical improvement should not be expected from the amebicidal treatment of carriers. All carriers of Endamoeba histolytica should be rid of their parasites for public health reasons and to avoid the possibility of later complications in themselves.

### American Journal of Medical Sciences, Philadelphia

**198:** 445-588 (Oct.) 1939

Islet Cell Tumors of Pancreas. W. R. Campbell, R. R. Graham and W. L. Robinson, Toronto.—p. 445.
*Should Digitalis Be Administered to Patients with Preexisting Partial Heart Block? H. L. Blumgart and M. D. Altschule, Boston.—p. 455.
Experimental Arthritis in Rabbits Produced with Streptococci and Other Organisms. R. L. Cecil, D. M. Angevine and S. Rothbard, New York.—p. 463.
Clinical Experience with Globin Insulin. L. Bauman, New York.—p. 475.
*Prediction and Prevention of Late Pregnancy Accidents in Diabetes. Priscilla White, R. S. Titus, E. P. Joslin and Hazel Hunt, Boston.—p. 482.
*Erythropoiesis Following Bleeding Peptic Ulcer. R. H. Lyons and C. Brenner, Boston.—p. 492.
*Cystine Hydrochloride as Anticoagulant for Clinical Use. T. J. Putnam and P. F. A. Hoefer, Boston.—p. 502.
Study of Clotting Defect in Hemophilia: Delayed Formation of Thrombin. K. M. Brinkhous, Iowa City.—p. 509.
Blood Studies in Lymphogranuloma Venereum; with Special Reference to Serum Proteins. R. H. Kampmeier, D. W. Smith and R. M. Larsen, Nashville, Tenn.—p. 516.
Studies on Phytotoxic Index: III. Evaluation of Method with Reference to Depressed Psychotic Patients. J. M. Looney, W. Freeman and Rose R. Small, Worcester, Mass.—p. 528.
Electrocardiogram During Insulin Shock Treatment of Schizophrenia and Other Psychoses. S. Bellet, H. Freed and W. W. Dyer, Philadelphia.—p. 533.
Fecal Impaction. K. W. Benson and J. A. Bargen, Rochester, Minn.—p. 541.
Origin of Ammonia in Urine Under Normal Circumstances and in Kidney Disease. M. Friedenson, New York.—p. 546.
Chromium Poisoning in Infancy. J. F. Sander, Lansing, Mich., and C. D. Camp, Ann Arbor, Mich.—p. 551.

**Digitalis and Partial Heart Block.**—Because of conflicting opinions as to whether digitalis should be given to patients with partial heart block, Blumgart and Altschule observed its effect on nineteen patients from 15 to 72 years of age with congestive heart failure. Digitalis was administered in doses calculated on the basis of body weight; somewhat less than the full Eggleston dosage was administered. Digitalization was accomplished within three to nine days. Nausea was induced in six cases and in these no significant change in PR interval occurred. In two of these cases, changing 2 to 1 and 1 to 1 responses were present before and after digitalization. Of the nineteen cases studied, the PR interval did not change in eleven, in three a lengthening of 0.02 second and in three a lengthening of 0.04 second occurred, in one the PR interval was shortened by 0.04 second and in another the PR interval was shortened by 0.08 second. No alteration in the orderly sequence of auricular and ventricular contractions occurred except that observed in one case in which occasional 2 to 1 heart block disappeared and normal 1 to 1 response was established. The results demonstrate that digitalis in doses sufficient to induce therapeutic effects may be given in cases of partial heart block without causing interference with the orderly passage of impulses from the auricles to the ventricles. While digitalis and organic heart disease interfere with auriculoventricular conduction, these factors do not reinforce each other and their simultaneous presence does not lead to an additive effect when such doses as used in the present study are utilized. Although digitalis in doses of from 0.1 to 0.23 Gm. to 10 pounds (4.5 Kg.) of body weight did not greatly increase preexisting heart block in any case of this series, it is impossible to preclude the possibility that occasional or rare instances may be encountered in which this may occur, particularly if dosages approaching toxic amounts are employed. Therefore the authors warn that caution and careful observation should be exercised, particularly if larger doses than those employed by them are utilized.

**Pregnancy and Diabetes.**—From a study of the records of 353 pregnancies in 242 diabetic women cared for since 1898, White and her associates find that, excluding surgically inter-

rupted pregnancies, the fetal mortality in the preinsulin era was 44 per cent and in the insulin era 38 per cent. In the preinsulin era, early and late fetal deaths occurred with equal frequency. In the insulin era, 60 per cent of the fetal deaths were late because of stillbirth or neonatal accidents and 40 per cent because of spontaneous abortions. The authors believe that severe diabetic crises—coma and hypoglycemia—are not at all incompatible with the birth of a living child. Thus among fourteen accidents in late pregnancy maternal coma occurred only twice, in each instance precipitated by infection, and the remaining twelve patients had no signs of acidosis. The latter had taken meticulous care of their diabetes to ensure the birth of a living child. In contrast to this experience, other patients careless of the diabetic routine have had a successful outcome of the pregnancy. It became evident to the authors that stillbirth was not related to diabetes or its specific complication (coma) but was definitely related to preeclamptic toxemia and as time elapsed that the accidents—neonatal death and premature delivery—were also related to the abnormal hormone picture. The relationship of toxemia and stillbirth first became apparent to them when they observed that in many diabetic women the course of pregnancy was uneventful until the sixth month, when at any time thereafter edema, albuminuria and a rising blood pressure developed in the patient. Shortly after the rise of the blood pressure the fetus died and the signs of toxemia promptly disappeared. The entire clinical picture can occur and disappear in as short a time as one week, but it is predicted from four to six weeks by the rise of gonadotropic substance in the serum. Of thirty-five completed pregnancies studied for determinations of gonadotropic substance in the serum, nine were of former juveniles—patients with onset of diabetes before 15 years of age. In only one case did the onset of diabetes occur during pregnancy, and insulin was required in only one. Diabetes was severe or moderately severe in twenty-six. Coma developed in one case and hypoglycemia for three days in one, following the mistaken administration of 276 units of protamine zinc insulin. In general, the control of diabetes was good in all cases. The clinical course in the fourteen cases in which the values for serum gonadotropic substance were repeatedly normal was completely uneventful. Complications developed in the ten cases in which the values for serum gonadotropic substance were supernormal and no treatment was given. Toxemia developed in seven. Premature delivery occurred in the remaining three. In two successive pregnancies in the same case in which values for gonadotropic substance were supernormal but steadily fell the fall was preceded by a rise of estrogen four weeks prior to the normally expected time. During the first pregnancy well marked signs of toxemia developed. These decreased in severity with the fall of gonadotropic substance. Less well defined signs in the second pregnancy disappeared entirely. The biochemical behavior in this case gave further presumptive evidence of the probable value of estrogen therapy. Massive doses of estrogen were administered in nine cases in which the values for serum gonadotropic substance were supernormal, from 150,000 to 300,000 international units as progynon B being given and in addition progestin. Replacement treatment was followed by a drop in serum gonadotropic substance controlled by the size and frequency of the dose of estrogen. No instance of progressive toxemia occurred. Not one woman miscarried. There was a tendency for the serum protein which fell to low levels to rise without change in diet, the weight to fall, the urinary output to be increased, the albumin to be diminished and the blood pressure to fall. Therefore it seems that the test for gonadotropic substance permits one to classify the cases according to hazard and to gage the effect of therapy.

**Erythropoiesis Following Bleeding Peptic Ulcer.**—Lyons and Brenner evaluate, in 237 admissions of bleeding peptic ulcer, the problems presented by the anemia that follows hemorrhage. Special attention has been given to the symptoms resulting from the hemorrhage and the rate of recovery of the erythrocytes after the hemorrhagic episode. In all these cases there was either x-ray or postmortem evidence of peptic ulcer or a clinical diagnosis of a peptic ulcer based on typical symptoms of long duration or a definite history of melena or hematemesis either within a month before entry or during hospitalization. The authors found that the greater the anemia the greater was the average daily increment of erythrocytes. From average weekly erythrocyte counts it is seen that the erythropoietic response of the body is determined by the degree of the anemia at the moment and is independent of the initial severity of the hemorrhage itself. The observed erythropoietic rate for cases in this series, in the large majority of which a Sippy regimen was prescribed, was fully as good as that reported for cases in which a liberal "puréed diet" and iron were employed. Beyond the actual increment of donated cells, transfusion appears to have no effect on the rate of erythropoiesis. The net mortality for the series was 5.5 per cent. This appeared to be independent of sex or number of previous hemorrhages.

**Cystine Hydrochloride as Anticoagulant.**—Putnam and Hoefer state that the intracardial injection of cystine hydrochloride into dogs was followed by a rise in coagulation time of from 40 to 100 per cent in three of five experiments. The administration of cystine hydrochloride to dogs by stomach tube was followed by an increase of clotting time of from 25 to 100 per cent in all technically satisfactory experiments. Cystine hydrochloride also was administered by mouth in twenty-three cases in which the diagnosis of multiple sclerosis had been made. In seventeen a rise of coagulation time was observed, which varied from 30 to 90 per cent. Cystine hydrochloride is well tolerated by most patients in daily doses up to 3 Gm., over many months. No serious symptoms have been observed to follow its use. It is therefore suggested as an anticoagulant of rather low efficiency for use over long periods for conditions in which such an agent might be valuable.

## American Journal of Ophthalmology, St. Louis

**22:** 1071-1200 (Oct.) 1939

Ocular Shwartzman Phenomenon. T. E. Sanders, St. Louis.—p. 1071.
Studies on Surface Epithelium Invasion of Anterior Segment of Eye. T. L. Terry, J. F. Chisholm Jr., Boston, and A. L. Schonberg, Cleveland.—p. 1083.
Study of Methemoglobin Producing Organisms in Ocular Inflammations. M. A. Wood, Iowa City.—p. 1111.
Human Cyclopia with Associated Ocular Anomalies: Case Report and Embryologic Interpretations. I. E. Wilber, New York.—p. 1120.
*Irrigations with Sulfanilamide as Treatment for Gonorrheal Conjunctivitis: Report of Fifteen Cases. W. J. Rein and O. B. Tibbetts, Richmond, Va.—p. 1126.
Snake Venom in Ophthalmology. M. E. Alvaro, São Paulo, Brazil.—p. 1130.

**Sulfanilamide Irrigations for Gonorrheal Conjunctivitis.**—Rein and Tibbetts compare the results of fifteen cases of gonorrheal ophthalmia treated by earlier methods with those of fifteen cases treated with sulfanilamide irrigations. A special nurse irrigated the infected eye or eyes every fifteen minutes, night and day, with a 0.5 per cent solution of sulfanilamide made up in physiologic solution of sodium chloride. The amount of solution used in the irrigations varied, but an amount sufficient to keep the eyes clean was administered consistently. In cases in which other gonorrheal complications were present—vaginitis or urethritis—supplementary sulfanilamide, from 30 to 60 grains (2 to 4 Gm.), was usually given orally, according to the age and weight of the patient. At the end of twenty-four hours the cornea was usually cleaner and brighter, secretion of pus was almost stopped, edema of the lids was rapidly receding and when the complication of corneal ulcer was present the lesion advanced no further or began to heal. Smears were taken daily from the conjunctival sac, and the patient was discharged when three consecutive daily smears showed that intracellular or extracellular diplococci were absent. To date there have been no relapses. In the first fifteen cases the average number of days before a negative smear was obtained was 27.2, while in the fifteen treated with sulfanilamide it was 6.8 days. The sulfanilamide treatment was not abetted by additional therapy; the patients were given only adequate balanced meals and general care, together with attention to any coincidental complications. The economic advantages resulting from the reduced period of hospitalization compared to that required by other standard measures are obvious.

## Archives of Dermatology and Syphilology, Chicago

**40:** 687-866 (Nov.) 1939

Sencar-Usher Syndrome: Review of Literature and Report of Six Cases. U. J. Wile and H. L. Arnold Jr., Ann Arbor, Mich.—p. 687.
Nitritoid Reactions Due to Tryparsamide: Report of Case. F. A. Ellis, Baltimore.—p. 707.
*Flaccid Paraplegia Following Diagnostic Use of Frei Antigen. H. L. Keim and R. F. Wakefield, Detroit.—p. 709.
Pruritus Ani et Vulvae. Howard and Hugh Hailey, Atlanta, Ga.—p. 726.
Epidermodysplasia Verruciformis (Lewandowsky-Lutz). F. Wise and D. L. Satenstein, New York.—p. 742.
Pseudo-Atrophoderma Colli in Sisters. K. Frost, Los Angeles, E. Epstein, Oakland, Calif., collaborator.—p. 755.
Yaws: Five Hundred Cases Observed in Cuba. V. Pardo-Castello, Habana, Cuba.—p. 762.
Poikiloderma Atrophicans Vasculare: Report of Case. O. G. Hazel, Oklahoma City.—p. 776.
*Relation Between Syphilis and Tuberculosis in the Negro. S. Goldblatt, Cincinnati.—p. 792.

**Paraplegia After Use of Frei Antigen.**—Keim and Wakefield cite a case of flaccid paralysis which began eleven days after the intradermal diagnostic use of commercial mouse brain Frei antigen. Almost complete recovery had taken place four months later. The causative mechanism of these accidents is unknown. The authors feel that the cause must be sought not in the substances administered but in a constitutional predisposition of the person affected. The recent work on virus proteins and inapparent viruses suggests that altered virus activity might help clarify the nature of this individual susceptibility. The theoretical explanation offered is that after a period of incubation following nonspecific trauma of the skin (such as vaccination, injection, exanthems or virus eruptions) the patient responds with an interruption of his immunity by a reactivation of inapparent or latent viruses. This state of altered activity then leads to the production of paralysis and other unexplained clinical accidents.

**Syphilis and Tuberculosis in the Negro.**—As the literature concerning dual infection with syphilis and tuberculosis contains extremely divergent opinions, Goldblatt reviewed the records of 25,472 ambulatory Negro patients of all ages in an attempt to solve some of these difficulties. The diagnosis of syphilis was based on complete physical and routine serologic investigation of all applicants (by Wassermann, Kahn or Kline tests and usually by all three). Darkfield studies of doubtful open lesions and examinations of the spinal fluid of patients with suspected syphilis were carried out whenever possible. Serologic tests, including provocative procedures, were repeated whenever there was any reason to suspect the presence of syphilis. The diagnosis of tuberculosis was based on physical examinations together with fluoroscopic and x-ray studies of the chest. Investigation of the sputum for tubercle bacilli and guinea pig inoculations were made when the fluoroscopic and x-ray results did not confirm the physical observations. Necropsies were performed on 41 per cent of the patients who died (315), and the diagnosis of tuberculosis was confirmed in all cases in which section was done. Of the cases in which tuberculosis and syphilis were concomitant (186), anatomic evidence of syphilis was found in 34 per cent. It is probable that the distribution brought out by the investigation is representative of the Negro population of Cincinnati, as about half of the entire Negro population of the city came under observation. It was found that 33.7 per cent of the entrants to the clinic had syphilis either alone or combined with tuberculosis, whereas only 4.9 per cent came in with this specific complaint. Of the 2.5 per cent of patients diagnosed as having tuberculosis only 1.2 per cent were aware of their condition on entry. Tuberculosis was found in 318 (2 per cent) of the 16,919 patients without syphilis and in 326 (3.6 per cent) of the 8,556 patients with syphilis. Almost double (1.8 times) the amount of tuberculosis was found among the syphilitic as among the nonsyphilitic patients. Tuberculosis alone was more frequent in the younger patients than was syphilis alone. On the other hand, tuberculosis combined with syphilis (326 instances) was relatively more prevalent in the older age groups. Therefore the 310 patients who had contracted syphilis first must have contracted the tuberculosis at higher ages. It is shown that patients with syphilis are susceptible to tuberculosis at the higher ages to a much greater degree than are those who are free from the ravages of syphilis. Among nonsyphilitic persons tuberculosis enters at a maximal rate in the twenties, falling away at lower and at higher ages. Among syphilitic persons the incidence of contracting tuberculosis increases steadily with age to about the age of 40 and then appears to level off or to decrease somewhat. Mortality rates for tuberculosis were increased by the presence of associated syphilis, particularly when the latter was in a late active stage. Antisyphilitic treatment administered to patients with both tuberculosis and syphilis prolonged life. It appears that the control of syphilis among Negroes will assist substantially in the control of tuberculosis.

## California and Western Medicine, San Francisco

**51:** 217-288 (Oct.) 1939

Medicine in a Changing World. T. Parran, Washington, D. C.—p. 222.
*Boxer's Hemorrhage. J. L. Carr and A. M. Moody, San Francisco.—p. 227.
Intraspinal Protrusions of Intervertebral Disks: Roentgenographic Findings. K. S. Davis, Los Angeles.—p. 230.
Carcinoma of Prostate. F. Hinman and D. Smith, San Francisco.—p. 235.
Some Indications for Roentgen-Ray Treatment. U. V. Portmann, Cleveland.—p. 241.
Can Clinics Help Practitioners of Medicine? W. E. Carter, San Francisco.—p. 244.

**Boxer's Hemorrhage.**—Carr and Moody add three cases of hemorrhage to a case encountered by Moody in 1931 in which a boxer died after a severe beating. At necropsy scattered small contusion-like hemorrhages in the cortex, cerebellum and stem were found. The three present cases of contusion hemorrhages of the brain occurred in the stem after fisticuffs which produced no fracture of the skull or injury elsewhere in the brain, either cerebral or cerebellar. With the person, at least in the terminal stages of the beating, only partially conscious or, in the boxing terminology, "out on his feet," the musculature is more relaxed than normal, and muscle tone is definitely decreased. The motion of the head on the cervical vertebrae is more pronounced than during the usual state, and more acute angulation of the brain stem is possible on flexion and extension of the head. Because in the three cases that the authors encountered hemorrhage occurred in connection with fisticuffs of some nature, the specific and limited injury is regarded as peculiar to boxers or fighters—to those who are involuntarily beaten or in whom the type of injury causes acute angulation and pinching of the pons and medulla over the tentorium. The term "boxer's hemorrhage" is suggested for these injuries.

## Florida Medical Association Journal, Jacksonville

**26:** 161-212 (Oct.) 1939

Some Considerations of Hyperthyroidism from Medical Point of View. W. Merritt, Jacksonville.—p. 171.
Surgical Aspects of Hyperthyroidism. W. D. Owens, Miami Beach.—p. 175.
Prognosis in Heart Disease. J. G. Seltzer, Orlando.—p. 180.
Review of Syphilis at the State Hospital. J. C. Robertson, Chattahoochee.—p. 186.
Common Foot Ailments. E. W. Cullipher, Miami.—p. 189.

## Illinois Medical Journal, Chicago

**76:** 301-392 (Oct.) 1939

Carcinoma of Larynx. L. B. Bernheimer, Chicago.—p. 319.
Efficient Adjunct in Treatment of Corneal Ulcer. W. W. Gailey, Bloomington.—p. 322.
Gastrointestinal Symptoms of Respiratory Infections in Children. J. F. Carey, Joliet.—p. 325.
Cooperation of County Secretaries with Scientific Service Committee. R. S. Berghoff, Chicago.—p. 329.
Cataract versus Glaucoma. L. Bothman, Chicago.—p. 331.
Rabies Control in Illinois. C. A. Z. Sharp, Springfield.—p. 335.
Excretion Urography: Comparison with Retrograde Pyelography. A. E. Jones and R. A. Arens, Chicago.—p. 339.
Technic of Radium Treatment of Radiosensitive Neoplasms Involving Anterior Vaginal Wall. F. E. Simpson, collaborators J. E. Breed and J. S. Thompson, Chicago.—p. 344.
Control of Syphilis and Gonorrhea in State of Illinois. H. M. Soloway, Springfield.—p. 346.
Modern Changes in Plastic and Reconstructive Surgery of Face and Neck. M. R. Guttman, Chicago.—p. 349.
New Management for Relief of Angina Pectoris and Coronary Disease. O. A. Strauss, Chicago.—p. 351.
Half a Million Deaths from Appendicitis. A. S. Jackson, Madison, Wis.—p. 355.
Everyday Problems in Gynecology. L. Brady, Baltimore.—p. 357.
Late Obstetric Hemorrhages as Cause of Maternal Mortality in Chicago During 1938. C. Newberger, Chicago.—p. 368.
Undulant Fever: Its Sources, Modes of Infection and Prophylaxis. J. F. Shronts, Woodstock.—p. 373.
Interauricular Septal Defect (Primitive Ostium Primum) Associated with Mitral Stenosis (Lutembacher's Syndrome) and Syphilitic Aortitis. J. D. Kirshbaum and L. Perlman, Chicago.—p. 380.
Obstetric Analgesia, Anesthesia and Amnesia. E. Nash, Galesburg.—p. 383.

## Journal of Bacteriology, Baltimore

**38:** 355-484 (Oct.) 1939. Partial Index

Studies on Capsule Formation: I. Conditions Under Which Klebsiella Pneumoniae (Friedländer's Bacterium) Forms Capsules. J. C. Hoogerheide, with technical assistance of Madeline H. Harrison, Philadelphia.—p. 357.
Evaluation of Germicides by Manometric Method. J. O. Ely, Philadelphia.—p. 391.
Chemical Factors Influencing Growth of Tubercle Bacilli: II. Organic Reagents. B. C. Sher and H. C. Sweany, Chicago.—p. 411.
Lack of One of Somatic Antigens of Typhoid Cultures. Lois Almon and W. D. Stovall, Madison, Wis.—p. 419.
Colony and Antigenic Variation in Klebsiella Pneumoniae Types A, B and C. W. A. Randall, Washington, D. C.—p. 461.

## Journal of Pharmacology & Exper. Therap., Baltimore

**67:** 127-256 (Oct.) 1939. Partial Index

Nicotinic Acid and Vitamin B Complex in Insulin Tolerance. J. C. Burke and A. R. McIntyre, Omaha.—p. 142.
Influence of Disulfanilamide on Experimental Influenza Infections. D. R. Climenko, M. L. Crossley and E. H. Northey, Bound Brook, N. J.—p. 201.
Effects of Sulfanilamide on Lower Vertebrates. J. T. Litchfield Jr., Baltimore.—p. 212.
*Physiologic Adaptations in Cardiac Slowing by Digitalis and Their Bearing on Problems of Digitalization in Patients with Auricular Fibrillation. H. Gold, N. T. Kwit, H. Otto and T. Fox, New York.—p. 224.
Studies of Certain Addiction Characteristics of (*a*) Dihydromorphine (Paramorphan), (*b*) Dihydrodesoxymorphine-D (Desomorphine), (*c*) Dihydrodesoxycodeine-D (Desocodeine) and (*d*) Methyldihydromorphinone (Metopon). C. K. Himmelsbach, Lexington, Ky.—p. 239.
Effect of Fluidextract of Ergot and of Ergotamine on Emptying Time of Human Stomach. E. J. Van Liere and C. K. Sleeth, Morgantown, W. Va.—p. 250.

**Cardiac Slowing from Digitalis in Auricular Fibrillation.**—Gold and his colleagues studied the mechanism of cardiac slowing due to digitalis in ten patients with auricular fibrillation. Within a certain range of dosage the level of the ventricular rate in a given individual with auricular fibrillation may not reveal which of the two mechanisms (vagal abolished by atropine and extravagal not abolished by atropine) predominates, for the control of the rate may pass from the vagal to the extravagal factor as the dose is increased and in the reverse direction as the drug is eliminated, without a conspicuous change in the ventricular rate. This is due to reflex changes in vagal tone which play an important part in the ventricular slowing by digitalis in auricular fibrillation. An increased vagal tone in one stage of the action of digitalis and a decreased vagal tone after more intensive digitalization are the results of reflex adjustments. Depression of the vagus as a significant factor in the action of digitalis has not been considered heretofore. The results of the study suggest that the dose of digitalis should be reconsidered in the light of whether the vagal or the extravagal control of the ventricular rate is the more favorable mechanism for maintaining the optimal state of persons subject to auricular fibrillation and heart failure.

## Medical Annals of District of Columbia, Washington

**8:** 285-316 (Oct.) 1939

Carcinoma of Cervix. J. L. Southworth, Washington.—p. 285.
Hemophilia in the Negro: Report of Case. E. P. Campbell, Washington.—p. 294.
Diabetic Surgery at the Garfield Memorial Hospital from July 1, 1936, to Dec. 31, 1938. J. W. Lindsay, E. C. Rice, M. A. Selinger and K. H. Mish, Washington.—p. 296.
Gastroscopic Aspects of Chronic Superficial Gastritis. F. A. J. Geier, Washington.—p. 300.
Acute Benign Syphilitic Hepatitis: Report of Two Cases. G. W. Creswell, R. F. Golden and C. S. Coakley, Washington.—p. 303.

## Minnesota Medicine, St. Paul

**22:** 667-734 (Oct.) 1939

Principles of Fracture Treatment. C. L. Scudder, Boston.—p. 667.
Advances in Knowledge and Control of Cancer. L. Hektoen, Washington, D. C.—p. 671.
Keeping America Healthy. E. R. Coffey, Washington, D. C.—p. 677.
Medical Care and Its Distribution in Canada. F. W. Jackson, Winnipeg, Man.—p. 681.
Health of the People of Minnesota. W. A. O'Brien, Minneapolis.—p. 687.
The National Health Program. M. F. Griffin, Cleveland.—p. 688.
Health and the American Standard of Living. F. S. Chapin, Minneapolis.—p. 692.
Minnesota Medical Legislation. J. A. A. Burnquist, St. Paul.—p. 697.
Professional Service and the Public Trust. H. Shipstead, Minneapolis.—p. 701.
The Doctor and His Patient. G. Earl, St. Paul.—p. 703.

## New England Journal of Medicine, Boston

**221:** 593-634 (Oct. 19) 1939

Diverticula of Colon. L. A. Buie, Rochester, Minn.—p. 593.
Hydatidiform Mole and Chorionepithelioma. B. Tenney Jr. and F. Parker Jr., Boston.—p. 598.
*Use of Paredrine to Correct the Fall in Blood Pressure During Spinal Anesthesia. M. D. Altschule and S. Gilman, Boston.—p. 600.
Acute Lupus Erythematosus Disseminatus: Report of Case. A. W. Contratto and S. A. Levine, Boston.—p. 602.

**Paredrine for Fall in Blood Pressure in Spinal Anesthesia.**—Altschule and Gilman point out that paredrine (p-hydroxy-α-methyl-phenylethylamine hydrobromide), a drug recently introduced, has a powerful pressor action due to stimulation of the smooth muscle of the arterial wall and is effective when given by mouth, intramuscularly or intravenously. Good pressor effects are obtained with 20 or 30 mg. orally, 10 or 20 mg. intramuscularly and 5 or 10 mg. intravenously. These results suggested that the drug might be useful in correcting the fall in blood pressure observed during spinal anesthesia. The purpose of the present communication is to report the results obtained with paredrine in fifty cases. Measurements of pulse rate and blood pressure were made every five minutes; when the latter fell markedly, paredrine was administered in doses of 10 to 20 mg. intramuscularly or 5 to 10 mg. intravenously, or both. In every case the administration of paredrine was followed by a return of blood pressure to a satisfactory level. The pressure usually began to rise within five minutes after the intramuscular injection of 10 mg. of the drug; if no rise was noted at this time, a second injection of the same dose was given. This invariably secured the desired result. The authors conclude that paredrine is useful in raising the blood pressure to satisfactory levels if it becomes unduly lowered by spinal anesthesia. The pulse rate is maintained at, or returns to, levels obtaining before the induction of spinal anesthesia. Paredrine has little or no direct effect on the heart, its direct action being apparently limited to the peripheral vessels. No untoward effects have been noted after its administration.

## Oklahoma State Medical Assn. Journal, McAlester

**32:** 359-398 (Oct.) 1939

Pseudomycotic Leg Ulcers. J. F. Hamilton, Memphis, Tenn.—p. 359.
Conditions Involving External Ear. H. Evans, Tulsa.—p. 365.
Use of X-Ray in Obstetrics. P. N. Charbonnet and E. O. Johnson, Tulsa.—p. 371.
Infection in Extremities of Diabetics. W. D. Hoover, Tulsa.—p. 375.
Renal Emergencies. A. R. Sugg, Ada.—p. 377.

## Psychiatric Quarterly, Utica, N. Y.

**13:** 599-808 (Oct.) 1939

Some Unconscious Determinants in Homicide. P. R. Lehrman, New York.—p. 605.
Psychiatry and the Law—Cooperators or Antagonists? W. Overholser, Washington, D. C.—p. 622.
Blood-Cerebrospinal Fluid Barrier of Normal Children as Determined by Bromide Permeability Quotient. F. A. Mettler, M. Robinow, W. R. Brown and C. M. Burpee, Augusta, Ga.—p. 639.
Humor and Hypomania. I. H. Coriat, Boston.—p. 681.
*Depression as Chief Symptom. L. H. Ziegler, Wauwatosa, Wis.—p. 689.
Method for Differentiating Manic-Depressive Depressions from Other Depressions by Means of Parotid Secretions. E. I. Strongin and L. E. Hinsie, New York.—p. 697.
The Christian Formulation and Medicine. S. E. Jelliffe, New York.—p. 705.
*Value of Diphenyl Hydantoinate (Dilantin) in Psychoses with Convulsive Disorders. N. D. Black, Marcy, N. Y.—p. 711.
Contribution to Problem of Alcoholic Deterioration. J. J. Dorey, W. Hamburger and R. B. Sampliner, Utica, N. Y.—p. 721.
Personality in Alcoholic Disorders: Acute Hallucinosis and Delirium Tremens. N. J. T. Bigelow, S. R. Lehrman and J. N. Palmer, Utica, N. Y.—p. 732.

**Depression as Chief Symptom.**—Ziegler studied 111 patients whose first chief symptom consisted of well defined attacks of depression or low spiritedness. Their ages ranged between 16 and 77 years. Sixty-five were men. Essentially all occupations and the major professions were represented among them. Possessed of serious and sensitive natures, with a rigid singleness of purpose in their drives to succeed, they were not interested in hobbies and avocations. The majority leaned to the side of being introverted, self-centered persons. The onset of their depression was usually insidious and coincident with family trouble, financial loss, sickness or death. While depression was obvious enough when the patient consulted the surgeon or internist, it was not the earliest manifestation of the disorder for which relief was being sought.

This often proved to be a slowing up, a withdrawal from the usual activities, fatigue, loss of appetite and weight, and insomnia. Depression, worrisomeness, anxious concern about self, shame at the disorder, sadness, melancholy, despondency and low spirits usually appeared later to their fullest extent. Unusual and ofttimes mystifying bodily sensations were common, leading many of the patients from physician to physician and some finally to various creeds, cults and quacks. Firsthand data about thought and activity were ascertained only by friendly conversations and visits. Appraisals of thought, emotional state and activity are no less significant than ascites, heart murmurs or other signs of disease. These patients talked about themselves—out of all proportion to everything else. Not only was thinking slow, labored and limited in scope, but most of it was devoted to disagreeable topics which would correlate all too poorly with the actual events of life. Many patients traced the onset of the illness to the late winter or early spring months. The parents of many were of diverse temperament or personality makeup. The study of the previous lives of these patients shows the methods employed to cure the pathologic emotional state. When surgery was resorted to it tended to be directed to the thyroid. Even today goiter is too generally believed to be a cause of depression (often called nervousness). Mucous colitis or allergic phenomena were too readily accepted as causes when in reality they were more likely to be effects of the pathologic emotional state. These patients were grossly and quite universally misunderstood, which added much to their already great discomfort. Some of them were accused by relatives or friends of "putting on" their illnesses "or imagining them" and were upbraided for lack of self control. It is best for the patient of this type to go to a suitable sanatorium or hospital and, as far as possible, to make this step of his own volition. In treating these patients sleep was restored as far as possible by medicines and warm baths were used in moderation and were properly timed. Mild sedatives were given to relieve the daily distress, which is usually at its worst in the morning. The diet was organized so that lost weight tended to be regained. The hands were kept busy so that the patient had less chance to think of morbid things. Reasonable assurances of a favorable outcome were implied. The author has witnessed the recovery of depressed patients 75 years of age. He has also seen patients recover after being depressed for ten years or longer. But exact science has yet to evolve a specific method of cure, despite the startling immediate effects of metrazol and the claims for treatment with estrus-inducing products. From one to two years after treatment fifty-seven patients were heard from or were reexamined. Four had grown worse and two of these were in a state hospital. The condition of sixteen was unchanged. Thirty were improved and one of these was in a sanatorium. Seven were completely well. Forty-two were carrying on at their work as best they could. Since infectious diseases are on the wane, it behooves the next generation of physicians to learn more about the pathologic aspect of depression. The prevention of depressions, the author believes, should have a place in the public health programs of the future.

**Diphenyl Hydantoinate for Psychoses with Convulsions.**—Black used diphenyl hydantoinate for seventeen patients with psychoses and convulsions who had not reacted well to other forms of chemotherapy. Two patients had complete relief from seizures (a minimum of six months without a seizure) and seven others had a reduction in the number and severity of seizures. The remaining eight either were not influenced by the drug or showed an increase in the number and severity of convulsions. Mental improvement was in direct relationship to the control or reduction in the number of seizures. Treatment of one patient had to be discontinued because of toxic symptoms, and of three patients because of an increase in the number and severity of seizures. Ten are still receiving the drug. Three died. The author believes that the use of the drug should be restricted to patients who do not respond to less toxic forms of treatment.

## Rhode Island Medical Journal, Providence

**22:** 161-174 (Oct.) 1939

Metrazol Therapy at the Charles V. Chapin Hospital. H. E. Kiene, H. Miller and R. J. Streitwieser, Providence.—p. 161.

Results and Complications of Metrazol Therapy for Mental Disease. C. Rupp, Howard.—p. 164.

## Surgery, St. Louis

**6:** 491-652 (Oct.) 1939

Surgical Treatment of Acute Cholecystitis and Common Duct Obstruction. H. Finsterer, Vienna, Germany.—p. 491.

Solitary Nonparasitic Cyst of Liver. W. K. Jennings, Evanston, Ill.—p. 507.

*Maintenance of Nutrition in Surgical Patients, with Description of Orojejunal Method of Feeding. A. Stengel Jr. and I. S. Ravdin, Philadelphia.—p. 511.

Results of Intravenous and Intra-Arterial Administration of Fluids in Traumatic Shock Produced Experimentally. D. B. Kendrick Jr., Rochester, Minn.—p. 520.

*Acute Perforated Peptic Ulcers. M. W. Kelly, St. Louis.—p. 524.

Experimental Osteomyelitis: Effects on Ribs of Increased Intramedullary Pressure and of Toxin Producing and Non-Toxin Producing Strains of Staphylococci. R. D. Cressman and A. Blalock, Nashville, Tenn.—p. 535.

Tumors of Salivary Glands: I. Review of Prognostic Data from Literature. J. W. Houck, Richlands, Va.—p. 550.

Id.: II. Study of Forty-Eight Cases, with Presentation of New Clinical Classification. J. W. Houck, Richlands, Va.—p. 565.

Bathing Trunk Nevus. H. Conway, New York.—p. 585.

Esophageal Stenosis: Spontaneous Stricture in Young Child Followed by Spontaneous Opening One Year After Tubovalvular Gastrostomy. E. M. Miller, Chicago, and R. T. Bothe, Aurora, Ill.—p. 598.

Simplified Blood Transfusion Set. S. W. Widger and R. Stevens Jr., Rochester, N. Y.—p. 602.

Primary Tuberculous Peripheral Vascular Disease. T. Thieme and W. G. Maddock, Ann Arbor, Mich.—p. 604.

Simple Method of Applying Head Dressings. H. D. Cogswell and C. A. Thomas, Tucson, Ariz.—p. 610.

**Maintaining Nutrition of Surgical Patients.**—Stengel and Ravdin call attention to some of the dietary deficiencies of surgical patients. They describe the orojejunal method of feeding and discuss its advantages when there is no interference with the protein regenerating mechanism. It has been their experience that the early introduction of the feeding mixture into the distal jejunum results in the earlier return of peristaltic activity after operation. They have been impressed by the smoothness of the convalescence and by the fact that the patients do not request food, even though orojejunal feeding in some instances has been continued for as long as fourteen days after operation and the caloric intake has not been high. During this time, fluid and electrolyte balance, as a rule, can be maintained without resort to intravenous administration. This is of some importance, for phlebitis frequently occurs when prolonged intravenous therapy, especially with dextrose, is maintained. Frequently the injudicious intravenous use of large amounts of sodium chloride postoperatively precipitates edema when this complication would not have developed had nutrition been maintained and if the water and salt intake were not excessive. Too much emphasis has been placed on the fluid and salt requirements of these patients and too little on associated factors which play an important part in keeping fluids in the blood vessels. The method need not always be used, for not all patients have suffered prolonged nutritional deficits. It can be used, however, for every patient subjected to a gastro-enteric anastomosis when suction drainage is to be carried out after operation, for it simplifies the postoperative management since the nutritional requirements of the patient can be fulfilled more adequately.

**Acute Perforated Peptic Ulcers.**—A review of the diagnosis, treatment and results in 152 cases of acute perforated peptic ulcer treated surgically at the St. Louis City Hospital during a period of six years is presented by Kelly. All the patients were either on relief or unemployed. There were 124,317 general admissions to the hospital during the six years under study, giving an incidence of 0.0012 per cent of perforated peptic ulcers. Most of the perforations occurred in the middle years of life. All patients 70 or more years of age died. The number of cases that occurred during the four seasons was approximately the same, there being only a slight, but insignificant, increase during the spring and fall months. Only seven patients were women, 4.6 per cent. This ratio of men to women compares favorably with many other reports. A history of previous gastric disturbance was given by 128, or 84.2 per cent, of the patients. This fact indicates that previous gastric disturbances are a valuable aid in diagnosis. The duration of symptoms varied from seven days to fifty-five years. Twenty-four patients experienced the pain of perforation as the first symptom of their gastric disturbance. No relationship was

found between the duration of ulcer symptoms before perforation and the mortality rate. When the patient first experienced the pain of perforation, it was described by sixty-two as being in the epigastrium and general abdomen. The next most frequent location of the pain was in the epigastrium alone, fifty-two times. Generalized abdominal pain was described by twenty-three patients. Fifteen patients described their pain as occurring in the middle or lower part of the abdomen or at the upper right quadrant; 113 vomited after the perforation and before operation, while thirty-nine did not vomit. A study of the symptoms of perforated gastric and duodenal ulcers indicates that an anatomic location of the ulcer cannot be made from the history of the perforation. An acute perforation constitutes a surgical emergency and delay in operation increases the mortality rate. The author believes that the simplest and quickest operation should be performed in acute perforations and that the operation of choice is simple purse-string closure; frequently a tab of omentum was sutured over the closure. This procedure is used with the view in mind of preserving the life of the patient and seems to be attended by the least mortality. Only a small percentage of cases necessitated secondary operations, thus justifying the procedure. Of the 140 cases in which operation was performed drainage was instituted in 102 and the mortality rate was practically the same in the two groups. Thirty-nine, or 27.8 per cent, of the 140 patients operated on died. A postmortem examination was made in the twelve cases in which operation was not done. Three of the patients who were not operated on were more than 71 years of age and were in a moribund state on entry. They died soon afterward. Four were in extremely poor physical condition on entry and supportive measures were instituted, but the patients did not rally enough to justify operating. One patient who died shortly after admission did not have a diagnosis until the postmortem examination. Four incorrect diagnoses were made. The average stay in the hospital for the patients who recovered was 25.1 days. Of the postoperative deaths 51 per cent occurred within the first three days. A follow-up was made on fifty-seven of the 101 patients discharged. A patient was considered as having a good result if he was entirely free from pain and was able to work. A few of these patients remained on a diet. If the patient at times had pain which was easily controlled by a diet, the result was considered as fair. If ulcer symptoms were constant the results were considered poor. By these standards, forty-three were considered as having a good result, ten a fair result and four a poor result.

## Tennessee State Medical Assn. Journal, Nashville

**32:** 339-378 (Oct.) 1939

Clinical and Epidemiologic Features and Differential Diagnosis of Rocky Mountain Spotted Fever and Endemic (Murine) Typhus Fever. L. L. Lumsden and C. B. Tucker, Nashville.—p. 339.
Study of Infant Mortality in Tennessee, 1934-1937. J. M. Saunders and Ruth R. Puffer, Nashville.—p. 342.
Relationship Which Should Exist Between the Industrial Physician and the Private Practitioner of Medicine. C. F. N. Schram, Kingsport.—p. 350.
Some Phases of Anemias. R. E. Ching, Memphis.—p. 354.

## Texas State Journal of Medicine, Fort Worth

**35:** 385-450 (Oct.) 1939

Hemorrhage in Obstetric Patients. J. B. Pastore and H. J. Stander, New York.—p. 390.
Diaphragmatic Hernia. A. O. Singleton, Galveston.—p. 397.
Action and Uses of Castilian Malva Solution in Infectious, Necrotic and Gangrenous Lesions. R. P. Thomas Jr., San Antonio.—p. 403.
Rhabdomyosarcoma of Skeletal Muscle: Report of Two Cases. S. M. Richmond, San Angelo.—p. 407.
Treatment of Pneumonia in Children. J. Zahorsky, St. Louis.—p. 414.
Newer Methods of Treating Pleural Effusions and Tuberculous Empyema. H. M. Anderson, Sanatorium.—p. 419.
Diagnosis and Management of Allergic Rhinitis. M. C. Barnes, Waco.—p. 421.
Sarcoma of Uterus: Report of Case. D. R. Venable, Wichita Falls.—p. 425.
*Treatment of Drug Addicts at the United States Public Health Service Hospital, Fort Worth, Texas. W. F. Ossenfort, Fort Worth.—p. 428.

**Treatment of Drug Addiction.**—Ossenfort states that with the concept that drug addiction is the result of mental illness treatment at the Fort Worth (Texas) Public Health Service Hospital is divided into three main categories: (1) complete admission study of the patient as a whole to establish a base line in the individual case; (2) prolonged treatment on the basis of the initial observations throughout the remainder of the patient's stay in the hospital, and (3) adjustment of outside conditions in preparation for his eventual return to society. Since so many addicts are recruited from the more or less unstable portion of the population it is not anticipated that results will ever be uniformly successful. The physical condition of patients is always remarkably improved, and their power of resistance to influences that tend to cause a reversion to narcotics is strengthened in a large majority of cases. It is not hoped, however, to erase in all cases fundamental defects to the point at which they may not become manifest again when the afflicted person is subjected to severe environmental stresses. The results seem to justify the conviction that the management of drug addicts as patients who are mentally ill is logical. It is not believed that a long prison sentence is an aid to rehabilitation. The prevention of addiction among the unstable is only a part of a broad program of mental hygiene. Patients suffering from asthma or migraine are especially susceptible to addiction because of the recurrence of attacks. It is doubtful whether such persons should ever be given morphine. Morphine should never be used to tide a patient over the effect of an alcoholic spree. Thousands of persons have been made addicts by just such treatment. In painful conditions calling for an opiate it is best to start with codeine or, if morphine is at first necessary, to change to codeine as soon as possible. New opiates should be used with caution.

## Western J. Surg., Obst. & Gynecology Portland, Ore.

**47:** 561-610 (Oct.) 1939

*Gas Gangrene: Analysis of Thirty-Four Cases Treated in Past Five Years in San Francisco Hospital, with Special Reference to Roentgen Ray Therapy. A. J. Williams and H. V. Hartzell, San Francisco.—p. 561.
Factors Influencing Prognosis of Carcinoma of Colon. C. W. Mayo, Rochester, Minn.—p. 566.
Metastatic Malignancy in Bone: Absence of Roentgenographic Signs. H. Snure, Los Angeles.—p. 571.
Neglected Adenomas of Thyroid. R. W. Binkley, Selma, Calif.—p. 575.
Primary Eosinophil Adenocarcinoma of Hypophysis: Case Report. G. A. C. Snyder and C. P. Larson, Fort Steilacoom, Wash.—p. 581.
*Ovarian Hypofunction Previous to Climacteric: Report of 300 Cases Treated with Estrogen. L. F. Hawkinson, Oakland, Calif.—p. 584.
Further Observations on Fallacy of Use of Iodine Immediately After Bilateral Subtotal Thyroidectomy. M. Davison and L. J. Aries, Chicago.—p. 589.
Theory and Results of Prophylaxis of Endemic Goiter in Switzerland. H. Eggenberger and F. M. Messerli, Herisau, Switzerland.—p. 596.
Surgical Approach to Hypertension: Division IX. F. M. Findlay, San Diego, Calif.—p. 600.

**Gas Gangrene.**—Williams and Hartzell compare the results obtained in seventeen consecutive cases of proved gas gangrene in which roentgen therapy was administered with those of seventeen similar cases in which the treatment was not given. Cases in which there was bacteriologic proof alone without clinical proof were not included. Seven patients entering the Emergency Hospital who from the nature of their injuries might have developed gas gangrene were treated prophylactically and none had gas gangrene. Conclusions are not drawn from this group, but the authors believe that the possibilities of prophylactic treatment in such cases are suggested. In comparing the mortality rates of the two series the authors point out that of twelve traumatic cases in each group there is a difference of 50 per cent. The only fatality among the twelve patients who had roentgen therapy was of a patient practically moribund when the treatment was started. This patient died seven hours after the first treatment. There were also eight patients (four in each group), all of whom died with arteriosclerotic gangrene complicated by gas gangrene. At necropsy two of the untreated showed gas in the tissues but in none of the four that had been irradiated was there such evidence. Of two patients with diabetic gangrene complicated by gas gangrene, one received roentgen therapy and this was the only recovery in the complicated series. Of those irradiated, none died from gas gangrene; two died from pulmonary embolism, one from pneumonia and the other from arteriosclerotic heart disease. No gas gangrene was present at necropsy in these cases. This type of case constitutes a distinct entity and it is felt that these should not be grouped with the traumatic series. The authors believe that a rational

procedure in any given instance of compound fracture as the patient enters the hospital would be as follows: 1. Conservative surgery—adequate débridement should be done. 2. X-ray examination should be made to determine the extent of the injuries and the presence of gas in the tissues. 3. If gas infection is suspected another roentgenogram should be taken within six hours. 4. If there is clinical, bacteriologic or x-ray evidence of gas gangrene, roentgen therapy should be given at once and repeated at least once every twelve hours for three days.

**Ovarian Hypofunction Previous to Climacteric.**—Hawkinson discusses the results of estrogen therapy in 300 cases of menstrual disorders associated with ovarian underfunction. Patients with an artificial menopause and, when possible, those with the natural menopause were excluded. Also all patients whose symptoms might be accounted for by organic complications were eliminated. The patients' ages ranged from 14 to 35 years, with an average age of 27 years. The average duration of symptoms was fourteen months with the exception of thirty-four patients who complained of symptoms since the menarche. More than one third of the patients had symptoms soon after pregnancy or abortion and more than 12 per cent after salpingectomy or the removal of one ovary. The symptoms, as in the menopausal syndrome, are due primarily to a deficiency of estrogen and, with the exception of the menstrual disturbances and the changes in the vaginal smears, are of a subjective nature. Nervousness was an almost constant complaint but was seldom objective in type. Fatigability and lassitude were almost as prevalent as nervousness. Almost 40 per cent had disturbances of sleep. Excitability and irritability, reflected by exaggerated response to slight emotional shocks, were common. Gastric disturbances, cardiac symptoms and vague and indefinite pains occurred in many cases without demonstrable pathologic changes. The most common cardiac symptoms were palpitation and tachycardia. Flushes and chills were complained of by 18 per cent of the women. Headaches were complained of by 46 per cent of the patients. Of the 265 who had definite menstrual disturbances, 174 suffered from scanty menstruation. Eighty-nine had dysmenorrhea and an almost equal number had irregular menstruation. Menorrhagia, metrorrhagia and secondary amenorrhea were not as common. A number of patients had two or more disorders of menstruation. Many patients stated that there was a difference in the intensity of the symptoms month by month, suggesting the involvement of one ovary. Only standardized estrogenic preparations were used in treatment. The amount of estrogen required to relieve symptoms varied with each patient. Some patients responded to oral therapy alone, while others required as much as 10,000 international units (2,000 rat units) of estrogen in oil by hypodermic injection three times weekly. Initially the oral preparations were usually administered. If there was no response within three to four weeks, larger doses of estrogen in oil were administered intramuscularly. Combined oral and hypodermic therapy was of advantage in the severe cases. After a satisfactory response had been obtained, the dose was gradually reduced, and only when the patient remained free from symptoms was it discontinued. The average patient required treatment for three or four months. However, fifty-seven women required continuous oral treatment to remain symptom free. With the exception of an occasional local reaction at the site of injection, no ill effects were observed. The subjective symptoms responded more favorably than did the associated menstrual disturbances. Data show that 44.3 per cent were relieved of the majority of symptoms, 31 per cent were improved and 24.7 per cent experienced little or no relief. Forty-four patients (74.5 per cent) found that estrogen decreased the severity and frequency of attacks of menstrual migraine. Fourteen (31.8 per cent) obtained complete relief from headaches. Of the seventy-eight women who complained of occipitocervical aching, sixty-one were relieved. Of the fifty-four patients who had a low hemoglobin with or without a corresponding decrease in the number of erythrocytes, twenty-nine (57.4 per cent) showed improvement in the hemoglobin level and number of erythrocytes following the administration of estrogen. The majority had experienced difficulty in maintaining an improved level with liver and iron therapy.

## FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

### Australian J. Exper. Biol. and M. Science, Adelaide

**17:** 225-332 (Sept.) 1939. Partial Index

Tissue Injury by Volatile and Gaseous Anesthetics. C. H. Kellaway and E. R. Trethewie.—p. 225.

Poliomyelitis: I. Intra-Ocular Inoculation as Standard Method for Demonstration of Neutralizing Antibodies. F. M. Burnet, A. V. Jackson and E. G. Robertson.—p. 253.

*Id.: II. Significance of Neutralizing Antibodies in Human Serums. F. M. Burnet and A. V. Jackson.—p. 261.

Passive Immunity in Experimental Pertussis. E. A. North, E. V. Keogh, G. Anderson and S. Williams.—p. 275.

Biochemical Changes Occurring During Storage of Human Blood. Marjorie Bick.—p. 321.

**Neutralizing Antibodies of Serums in Poliomyelitis.**—Burnet and Jackson tested the serums of fourteen patients with clinical poliomyelitis and contacts of these patients for neutralizing antibodies. Of the children with the disease, five possessed antibody at the time of the acute illness. The other nine had insufficient antibody for neutralization and eight of these even when convalescent still had insufficient antibodies for neutralization. Of fifteen contacts six possessed antibodies, nine did not. Therefore it is seen that serums show no indication of an increase in serum antibody as a result of (or concomitant with) infection or contact. Some of the children with paralytic poliomyelitis had antibodies at the onset of the disease, while others who had none at the onset still had none some months later. In summary, children in the early stage of acute paralytic poliomyelitis may possess relatively large amounts of circulating antibody or they may have none. In those who have none, none develops within two to three months, in the experience of the authors. It has been assumed that the antibody against poliomyelitis virus which is present in most adult serums results from subclinical infection with the virus at those times when the disease is prevalent in the community. There is fairly substantial evidence that a smaller percentage of adults living in isolated rural communities possess poliomyelitis antibody than is the case in urban populations. The authors state that their results, which are consistent with those of Brodie and others (1937), are completely opposed to such a view unless the unlikely assumption is made that antibody first appears more than a year after the immunizing infection. In monkeys recovering from experimental poliomyelitis antibody appears as a rule from four to eight weeks after infection, and its activity is much lower than that of the average human adult serum. They believe that the best interpretation of the facts is that in human beings the poliomyelitis virus infects only nervous tissues and that in most cases little virus or antigenic material derived from it passes to the antibody-producing cells of the body. Therefore there is no significant appearance of circulating antibody in most instances. Since antibody obviously of specific origin can be obtained in monkey serum after infection, and since certain methods of human vaccination are reported to produce antibody in children, the possibility that a small proportion of individuals do produce antibody after poliomyelitis must be left open, but such production cannot possibly account for the occurrence of relatively high titer antibody in a majority of human beings more than 10 years of age. The orthodox view is that this antibody is a result of a process of widespread latent immunization by subclinical infections with the specific virus. There is no direct evidence in favor of this hypothesis. If specific immunization is excluded there seem to be three possible alternatives for the origin of "poliomyelitis antibody" in human serum: 1. It may develop as a result of a nonimmunologic change in serum globulin, which develops with age in the absence of antigenic stimulus. 2. It may be the response to some commonly encountered antigen which has determinant groups in common with the poliomyelitis virus. The antigen must reach the antibody-producing cells in considerable amount and hence is likely to be derived from a micro-organism which has some invasive power but is not a strictly neurotropic virus. 3. The antibody is a nonspecific or group antibody, appearing as a result of repeated infections with various micro-organisms not necessarily related antigenically to poliomyelitis virus. Of these alternatives it seems to the authors that the second is the most likely and that the antigenic stimulus evidently should be looked for among the micro-organisms (bacteria or viruses) which produce common minor infections.

## British Medical Journal, London

**2:** 753-794 (Oct. 14) 1939

Weil's Disease in the Northeast of Scotland: Account of 104 Cases. L. S. P. Davidson and J. Smith.—p. 753.
*Antirachitic Value of Human Milk. J. C. Drummond, C. H. Gray and N. E. G. Richardson.—p. 757.
Pathology of Chloride Metabolism in Man. A. Lyall.—p. 760.
Notes on Psychiatric Casualties of First Days of War. G. Pegge.—p. 764.
*Diabetes and Kidney Failure. K. E. Barlow.—p. 765.

**Antirachitic Value of Human Milk.**—According to Drummond and his associates, the mean antirachitic potency of the milk yielded by women on diets supplying in all probability from 100 to 250 international units of vitamin D daily and that of the milk from women given large amounts of vitamin D during the latter half of pregnancy indicates that 10 international units per hundred cubic centimeters of breast milk represents about the normal maximal value. Possibly the same evidence can be put forward to indicate that an intake of about 200 international units represents the minimal daily requirement of the nursing mother. The large doses of vitamin D given to some of the mothers over several months of pregnancy failed to bring about anything approaching a proportional increase in the vitamin D content of the milk. It may be, therefore, that there is an optimal concentration of this substance regulated by the mammary gland. The reason that the assimilation of the bone forming elements is better (from 40 to 60 per cent) when the child is fed on mother's milk than when cow's milk is used (from 20 to 30 per cent) has not yet been determined, but it may be important that the calcium-phosphorus ratio of human milk approximates that of bone mineral, the calcium-phosphorus ratio of cow's milk being considerably smaller. The relatively small concentration of calcium and phosphorus (from 27 to 34 mg. of calcium and from 13 to 17 mg. of phosphorus per hundred cubic centimeters of milk) in human milk as compared with cow's milk (from 100 to 160 mg. of calcium and from 70 to 100 mg. of phosphorus) raises several curious problems, of which the most important has been revealed by the careful studies of Leitch (1937), who has shown that the total intake of calcium when mother's milk is taken, much less the quantity actually retained, is often insufficient to provide the amount calculated as being requisite to maintain the composition of the body either at the maximal figure of 10 Gm. of calcium per kilogram of body weight or at the smaller estimate of 8.13 Gm. This observation led Leitch to consider the possibility that breast-fed infants must often exhibit not only imperfect calcification of new matrix but also osteoporotic changes in bones which at birth were relatively firm. It may be a fact that undetected rachitic changes are much more common in breast-fed infants than is suspected (Maddox, 1932). The authors state that there seem to be only two explanations for Leitch's figures. Either the newborn infant carries a reserve store of calcium sufficient to provide for adequate calcification during the months when the mother's milk does not provide enough or the data of the metabolism experiments which Leitch has used for her analysis are misleading, perhaps because the milk was not of such a quality as to favor optimal calcium retention. It remains uncertain in view of the evidence reviewed by Leitch whether changes in the dietary intake of calcium or phosphorus are reflected to any significant extent in the composition of mother's milk. The authors' results suggest that such an effect is not detectable, at all events in the first two or three months of lactation. Some of the mothers that they observed had been receiving about 2 Gm. of calcium lactate daily during the latter half of pregnancy, but this supplement to calcium-deficient diets did not appreciably influence the calcium content of their milk. There is need for more information not only about the composition but also about the yield of milk from mothers whose diet, adequate in all other respects, provides at least 2 Gm. of calcium, 1.5 Gm. of phosphorus and 300 international units of vitamin D daily. If such milk were made the subject of metabolic investigation on infants it is possible that some of the disturbing discrepancies would be dispelled.

**Diabetes and Kidney Failure.**—Two cases in which diabetes and nephrosclerosis coexisted are cited by Barlow. The evidence has obvious bearings on insulin therapy. In uncomplicated diabetes, glycosuria may be taken as evidence of a raised blood sugar level which may require to be lowered by insulin. In the nephritic patient, glycosuria has not the same significance. It is likely to be present in cases in which the blood sugar is not raised to a degree likely to be toxic to cell function, and if insulin were to be pushed in these cases, under the guidance of urinary dextrose, it seems probable that dangerous and even destructive hypoglycemia might be induced. The logical conclusion is that, so far as the diabetes is concerned, the patient with mild diabetes is better off with nephritis than without it. Whether this supposition is borne out, time and observation will reveal.

## Journal of Endocrinology, London

**1:** 117-230 (Sept.) 1939. Partial Index

Separation of Follicle-Stimulating Fraction from Pituitary Gonadotropin. H. Rinderknecht and P. C. Williams.—p. 117.
Duration of Action of Certain Natural and Synthetic Estrogens When Administered Orally or by Injection. C. W. Emmens.—p. 142.
Effect of Sex Hormones, Cortin and Vasopressin on Water Retention in Reproductive Organs of Monkeys. S. Zuckerman.—p. 147.
Precipitins in Antigonadotropic Serums. M. Van den Ende.—p. 156.
Further Observations on Progonadotropic and Antithyrotropic Activity of Antiserums to Extracts of Anterior Pituitary Gland. I. W. Rowlands.—p. 177.
Direct Gynecogenic and Indirect Estrogenic Action of Testosterone Propionate in Female Rats. R. L. Noble.—p. 184.
Effects of Synthetic Estrogens and Carcinogens When Administered to Rats by Subcutaneous Implantation of Crystals or Tablets. R. L. Noble.—p. 216.

## Proceedings of Royal Society of Medicine, London

**32:** 1371-1550 (Sept.) 1939. Partial Index

Simple Ulcer of Esophagus and Short Esophagus. P. J. Briggs, R. C. S. Dick and A. Hurst.—p. 1423.
Autonomic Imbalance and Borderline States of Thyrotoxicosis. L. Martin.—p. 1424.
*Leukopenic Myelosis. R. B. Scott.—p. 1429.
Pathology of Tumors of Urinary Tract. W. D. Newcomb.—p. 1455.
Radiologic Diagnosis of Neoplasms of Urinary Tract. R. Williams.—p. 1467.
Some Problems in Surgery of Old Age. C. Frankau.—p. 1483.
Hemorrhagic Purpura (Essential Thrombocytopenia) as Complication of Excision of Rectum. J. P. Lockhart-Mummery.—p. 1488.
Ossification in Rectal Cancer. C. E. Dukes.—p. 1489.
Intestinal Diverticula. H. Edwards.—p. 1495.
*Ancient Pregnancy Tests in Light of Contemporary Knowledge. H. P. Bayon.—p. 1527.

**Leukopenic Myelosis.**—In this paper Scott uses the term leukopenic myelosis to describe a type of myeloblastic leukemia in which the number of leukocytes in the circulating blood is subnormal for the whole or the greater part of the course of the disease. It is one variety of the complaint to which that contradiction in terms aleukemic leukemia has been applied. It would be idle to suggest that the leukopenia implies a disease process in any fundamental way different from myeloblastic leukosis with a leukemic blood picture, but clinical and hematologic convenience makes a segregation of such cases desirable, for they frequently offer diagnostic difficulty. Leukopenic myelosis is not a rare disease; in the last four years twenty-two cases have been encountered (more than three times the number of analogous leukemic cases seen during the same period) and this paper is concerned with a brief review of the clinical and hematologic observations in this series. A table grouping the patients according to age and sex indicates that no age and neither sex is particularly susceptible. The disease is characterized by three cardinal symptoms: anemia, a hemorrhagic tendency and a liability to necrotic angina. It is possible to differentiate acute, subacute and chronic types. The main characteristic of all forms is a progressive anemia; in acute cases hemorrhagic phenomena and necrotic angina are common. The blood count is characterized by orthochromic or hyperchromic anemia, sometimes with reticulocytosis and erythroblastosis. Leukopenia may persist throughout the course, or a terminal leukemia may occur, especially in the chronic cases. The features of the differential count are the presence of myeloblasts, although the percentage may be below 5 and the hiatus leukaemicus. Thrombocytopenia usually indicates a rapid course. The clinicohematologic picture leukopenic myelosis may be mimicked more or less closely by pernicious anemia, aplastic anemia, granulocytopenia and the leuko-erythroblastic anemias. The sternal puncture, however, determines the diagnosis; it reveals a great preponderance of primitive myeloid cells, most frequently with a predominance of myeloblasts. In two cases evidence was found that the erythropoietic tissues shared in the hyperplasia.

## Archives des Maladies du Cœur, Paris

**32:** 769-848 (Aug.) 1939. Partial Index

*Vitamin $B_1$ Deficiency and Cardiopathies: II. Vitamin $B_1$ Deficiency in Pathogenesis of Cardiac Disturbances of Pregnancy. G. Bickel.—p. 769.
The Lian-Minot Electrocardiograph with Electrofluoroscopic Control. C. Lian and G. Minot.—p. 790.
Importance of Precordial Derivations and of Proof of Exertion in Electrocardiographic Diagnosis of Angina Pectoris. G. Michaelides.—p. 808.

**Vitamin $B_1$ and Cardiovascular Disorders of Pregnancy.**—Bickel saw a secundigravida aged 33 in her sixth month of gestation. Anamnesis of her first pregnancy revealed pernicious vomiting, significant loss of weight, palpitation, dyspnea and edemas of the extremities. Similar symptoms characterized also the first half of her second pregnancy with loss of weight from 132 to about 103 pounds (60 to 47 Kg.), pulse 130 beats a minute, the liver overlapping by three fingerbreadths the edge of the ribs, white soft edemas halfway up the thighs, absence of knee jerk and heel reflex, violent pains and formication in the legs. The electrocardiogram disclosed a ventricular complex of low voltage in derivations 1 and 2 and an inverted T wave in derivations 2 and 3. Daily intravenous injections of 50 mg. of vitamin $B_1$ produced immediate curative effects. Acetonuria and the edemas disappeared after the third day. Restoration of appetite was rapid; the pains in the legs ceased and the electrocardiographic testimony indicated normal conditions. However, vitamin $B_1$ therapy, reduced to a weekly intravenous injection, was continued until shortly before fetal maturity. At this time the patient weighed 127 pounds (57.6 Kg.) and the x-ray examination of the thorax showed normal heart dimensions. She gave birth to a healthy child. According to the author, cardiovascular disturbances may appear during pregnancy in women who previously were entirely free from them. They are likely to appear in connection with pernicious vomiting or toxicosis of the liver and show a tendency to acidosis and polyneuritic symptoms. Such disturbances may be due, at least in certain cases, to a vitamin $B_1$ deficiency caused by the intra-uterine needs of the child and the upset of the mother's metabolism. The parenteral administration of vitamin $B_1$ effective in certain pregnancy polyneuritides is equally effective, the author finds, in certain pregnancy cardiopathies.

## Presse Médicale, Paris

**47:** 1397-1412 (Oct. 11) 1939

Postoperative Progressive Cutaneous Gangrene. P. Wilmoth.—p. 1397.
Procaine Hydrochloride Infiltration of Stellate Ganglions in Nasal and Bronchial Asthma, Angina Pectoris and Several Other Syndromes of Neurosympathetic Instability. A. Malherbe.—p. 1398.
*Continuous Drip Transfusion. A. Grimberg.—p. 1399.

**Continuous Drip Transfusion.**—Grimberg shows that blood transfusion by means of the continuous drip, a method that was first introduced by Marriott and Kekwick, has caused a radical revision in the earlier conception of blood transfusion. Because of the extreme slowness with which the blood is introduced, continuous drip transfusion permits the administration of much larger quantities of blood than did the customary technic. The average duration of the drip transfusion is twenty-nine hours, but it has been continued for as long as sixty hours; the average quantity of blood administered by the continuous drip is 2,700 cc., but as much as more than 6,000 cc. has been given at one time. A quantity of 100 cc. is regarded generally as the best hourly quantity of blood. The author describes the technic of the method and shows diagrams of the apparatus. Evaluating the anticoagulants, he expresses the opinion that heparin is superior to sodium citrate in drip transfusion. He also discusses the indications for this method of blood transfusion, pointing out that Marriott and Kekwick recommended drip transfusion only for the treatment of the various types of anemia, of those due to hemorrhage as well as of those due to toxic, infectious, hemolytic, aplastic and other causes. Other investigators, however, are of the opinion that the method deserves a more extensive application. The author thinks that the chief indication for the drop by drop blood transfusion is to restore in the patient a normal hemoglobin content, whatever may be the initial form of anemia. It is particularly indicated when severe anemia makes doubtful the success of a required operation.

## Archivio per le Scienze Mediche, Turin

**68:** 395-488 (Oct.) 1939

*Erythroblastic Anemia of Cooley's Type. A. Francaviglia.—p. 395.
*Anatomy of Erythroblastic Anemia. F. Schiappoli.—p. 457.

**Erythroblastic Anemia in Children.**—Francaviglia reports five cases of erythroblastic anemia of Cooley's type in children ranging in age from 2 to 8 years. Two of the patients were brother and sister. The disease is of unknown etiology. It is familial and hereditary. As a rule it develops during early childhood. Clinically the disease is characterized by the development of more or less acute erythroblastic anemia, increase of the volume of the liver, spleen and heart and skeletal alterations. The somatic development of the patients is retarded. The face is of the Mongoloid, adenoid or Negroid types. In the cases reported by the author the disease developed during the first or second year of life. Acute erythroblastic anemia was of the hypochrome type, with anisocytosis, poikilocytosis and reticulocytosis. There was leukopenia. The number of normal erythrocytes was diminished. Immature erythrocytes were abundant in the blood. The resistance of the erythrocytes, both mature and immature, was increased in all cases. The erythropoiesis was increased (medullary hyperplasia) with predominant production of basophilic erythrocytes and reticulo-endothelioblasts. The main alterations of the bones, as shown by x-ray examination, were hypertrophic and structural changes of the cranial and facial bones, especially thickness of the diploe and striation of the cranial vault and a process of diffuse osteoporosis of the skeletal bones. A history of infection or parasitism, such as syphilis, tuberculosis, malaria or helminthiasis, did not exist in any of the patients. The author found that the resistance of the erythrocytes in the blood of the parent who transmits the disease as well as in the blood of the apparently normal brothers and sisters of the patients is increased. He also found that administration of a combined treatment of thyroid and liver extract and iron may prolong the life and improve the general condition of the patients who have atypical forms of the disease which follow a slow evolution.

**Erythroblastic Anemia.**—Schiappoli made an anatomopathologic study of two cadavers of children who died from erythroblastic anemia of Cooley's type. He found that the main alterations from the disease are (1) a process of general reabsorption of the bones with formation of new trabeculas, (2) diffuse hyperplasia of the reticulo-endothelial system, especially in the hemopoietic organs, and (3) hemolytic anemia, with increased medullary and extramedullary erythropoiesis. The author concludes that the disease is a hemo-osteopathy of unknown etiology, for the development of which constitution and familial predisposition are the main factors. The anatomopathologic aspects of the disease are proper. Moreover, the disease is not to be classified in any of the following groups: hemolytic jaundice, erythroleukemia, hematochromatosis and pure general hyperplasia of the reticulo-endothelial system.

## Archiv für Kinderheilkunde, Stuttgart

**118:** 1-64 (Sept. 26) 1939. Partial Index

Trypanocidal Substance in Serum in Scarlet Fever: Investigations on Partial Function of Liver in Children with Scarlet Fever. J. Ströder.—p. 1.
Normocalcemic Tetany. A. Giegel.—p. 11.
Value of Weltmann's Reaction During Childhood. S. Holik.—p. 13.
Necessity of Cooperation of Pediatrician in Prophylaxis of Dental Decay During Childhood. L. Petrik.—p. 19.
Pathogenesis of Glycogen Storage Disease. W. Goeters.—p. 26.
*Etiology of Pemphigus. Ilse Markolf and H. Knauer.—p. 39.

**Etiology of Pemphigus.**—Markolf and Knauer say that cases of pemphigus neonatorum occur in which none of the known micro-organisms can be demonstrated. They recently observed an epidemic of especially severe cases of pemphigus, some of which presented the aspects of erythrodermia exfoliativa. Moreover, in older children there occur cases with mild general symptoms, which could perhaps be classified with dermatitis herpetiformis Duhring. Finally there are cases which greatly resemble pemphigus vulgaris in adults and some of which present the aspects of pemphigus foliaceus or pemphigus vegetans. The authors think that these various forms of pemphigus suggest that not all cases have the same cause. They decided to investigate whether a virus might perhaps play a part in pemphigus. In their search for virus bodies they employed several methods

simultaneously; namely, Herzberg's method of staining slide preparations, the culture on the chorio-allantois of hen eggs that had been incubated for several days, and animal experiments. They used these different methods on materials from six patients with pemphigus (three nurslings and three adults), whose histories are described in detail. Moreover, studies were made also on nurslings with various types of bullous disorders, but in all of these the results were negative. The authors observed elementary bodies suggestive of virus in the slide specimens of three of the aforementioned six pemphigus patients; that is, in two of the children and in one of the adults. However, in only one of these three cases in which the slide specimens yielded the suspected bodies could the same bodies be observed in the chorio-allantois culture. The animal experiments all produced negative results. The authors think that these negative animal experiments do not necessarily speak against a virus origin of pemphigus. They emphasize that the bodies, which they observed in the three cases, greatly resemble the Paschen bodies of smallpox. As a possible explanation that the suspected bodies were not detected in the other three cases, the authors suggest that studies may have been made at a time when the virus was no longer demonstrable or the bodies may have escaped observation. They concede that their investigations did not definitely clarify whether virus is a causal factor in pemphigus. Nevertheless they think that further investigations in this direction are justified, and they think that virus may be an etiologic factor at least in some cases of pemphigus.

## Fortschritte a. d. Gebiete der Röntgenstrahlen, Leipzig

**60:** 107-198 (Aug.) 1939. Partial Index

Morphology and Genesis of Dwarfism. W. Ecke.—p. 107.
Congenital Skeletal Anomalies of Lumbosacral Region in Cryptoscoliosis. R. Kienböck.—p. 134.
X-Ray Perspective and Its Transformation by New Technic of Exposure. K. Heckmann.—p. 144.
Foundations of Kymography of Heart. K. Heckmann.—p. 158.
Serial X-Ray Examinations on Miners of Joachimsthal Radium Mines. E. Saupe.—p. 163.
*Roentgenologic Observations in Chronic Amebic Dysentery. F. Meves.—p. 175.

**Roentgenologic Aspects of Chronic Amebic Dysentery.**—The patients examined by Meves had contracted amebic dysentery years before and had undergone one or several series of treatments. The majority presented the aspects of subchronic or chronic amebic dysentery, and others had late relapses of amebic infection. They were subjected to a thorough clinical examination. Parasites were searched for, and a rectoscopic examination was performed regularly. This was followed by roentgen study, which was done with the aid of the usual contrast mediums. The author reviews the intestinal changes observed by others in the course of amebic dysentery and compares them with his own observations. He emphasizes that roentgenoscopic examination of the colon during the subchronic and chronic forms of amebic dysentery frequently shows, in addition to well known aspects, the signs of a segmentary colitis; that is, different sections of the colon are diseased, and these are separated by unimpaired sections. The diseased portions show considerable atonia. The author thinks that the segmentary form of colitis is characteristic of amebic dysentery but not pathognomonic. He stresses that in relapses of amebic dysentery, x-ray examination is an indispensable diagnostic aid, because it helps to exclude other diseases of the colon.

## Klinische Wochenschrift, Berlin

**18:** 1141-1172 (Aug. 26) 1939. Partial Index

Sulfanilamides, Sulfapyridines and Their Derivatives in Treatment of Epidemic Cerebrospinal Meningitis. G. Säker.—p. 1141.
*Familial Investigations of Panmyelophthisis. H. Huber.—p. 1145.
Clinical Appraisal of Pulse Wave Rapidity. F. Herzog and H. Meurer.—p. 1150.
Etiology of Retinitis in Diabetes Mellitus. E. Heinsius.—p. 1153.
Successful Treatment of Carcinomatous Metastasis with Colchicine and Roentgen Ray Irradiations: Case. F. T. von Brücke and E. F. von Hueber.—p. 1160.

**Familial Panmyelophthisis.**—Huber made hematologic examinations of sixty-eight consanguineous relatives of four patients who died from panmyelophthisis in spite of intensive treatments with blood transfusions, liver extract, iron and vitamin C. The author was led to assume a bone marrow diathesis in the absence of any endogenous or exogenous agent in three of the four cases. The fourth case concerned a chemigrapher whose disease was attributable to an occupational poison. Familial investigations disclosed no involvements, though a sternal puncture was performed on seven of the eleven members of this group. Huber explored the erythrocytic and especially the leukocytic blood picture of these sixty-eight persons, including a differential and a blood platelet count. Setting the low level appraisal of leukopenia at 4,000 leukocytes and that of granulocytopenia at 2,500 neutrophils, he found that the leukocyte count never fell below 4,000 in the persons examined but that a significant modification of the granulocytes manifested itself in an imbalance between neutrophilic and lymphocytic cellular representation. The blood analysis of nine of the twenty-three kin of the first patient (a sister, her two sons, another nephew, a grandniece, a grandchild and three whose propinquity is not specified) indicated granulocytopenia or elevated lymphocyte percentages with the following differential imbalance ratios (sister omitted): 39.5 per cent neutrophils against 47.5 per cent lymphocytes; 40.5 against 46.5; 27.5 against 65; 29 against 55; a granulocytopenia of 2,352 neutrophils in the grandchild; 39.5 per cent neutrophils against 47.5 per cent lymphocytes; 47.5 against 44.5, and 47.5 against 45. Reexamination of the six specified kin six months subsequently, according to the author, showed a continued decrease of the neutrophils in all six. The hematologic study of sixteen family members of the second patient likewise disclosed granulocytopenia or imbalance of neutrophils and lymphocytes or both in seven (a brother and his three children, another brother, a sister and a grandniece), as the following analysis shows: 39.5 per cent neutrophils against 52.5 per cent lymphocytes; an anemia of 3,800,000 erythrocytes and 75 per cent hemoglobin in one of the three sons; 35 per cent neutrophils against 52 per cent lymphocytes; 31.5 against 54.5; 46 against 50; 46.5 against 46.5, and 46.5 against 47. The blood count of eighteen relatives of the third patient evidenced a similar pathologic condition of the blood in six (three sons of the youngest brother, a daughter and two others whose degree of relationship is not mentioned): 42 per cent neutrophils against 50 per cent lymphocytes; 46 against 50; 37 against 55; 42 against 50; 48 against 45, and 49.5 against 45.5. The author believes that a familial diathesis to bone marrow inferiority can be traced in cases of panmyelophthisis. Pathologic modifications affect the leukocytic blood picture and are charatcerized by an imbalance of neutrophil and lymphocyte cells. The pathognomonic aspects of the leukocytic picture are compatible with a normal erythrocytic status and a blood platelet count that shows no abnormally low levels. He thinks that hematologic divergences as uniform as those discovered in this investigation do not occur in healthy families and may be regarded as indicative of a congenital and inheritable bone marrow weakness.

## Medizinische Welt, Berlin

**13:** 1217-1252 (Sept. 2) 1939. Partial Index

Alimentary and Postinfectious Anemias of Childhood. H. Opitz.—p. 1217.
Concurrence of Angina Pectoris and Cholecystopathy. O. Bieling.—p. 1227.
Prophylactic Treatment of Hypertrophy of Prostate by Endocrine Means. H. Boeminghaus.—p. 1228.
*Signs of Intoxication After Use of Smallest Quantities of Atropine. W. Müller.—p. 1230.
Experiences with Digitalis Lanata. G. Schumacher.—p. 1231.

**Intoxication Caused by Small Doses of Atropine.**—The three cases of atropine intoxication described by Müller are noteworthy because of the small doses which elicited the symptoms of poisoning. In the first patient, a man aged 36, signs of intoxication developed after a quantity of ointment was introduced into the conjunctival sac, which contained from 0.5 to 1 mg. of atropine, from 1 to 2 mg. of scopolamine and from 0.5 to 1 mg. of cocaine. The author thinks that the toxic action was elicited chiefly by atropine and scopolamine. In the second patient, a boy aged 6, somatic and psychic signs of intoxication developed after conjunctival administration of atropine and homatropine in a total quanity of 0.25 mg. In the third patient toxic symptoms developed after he had taken 0.7 mg. of atropine in tablet form, and two days later signs of intoxication recurred when 0.2 mg. of homatropine was introduced into his eyes. On the basis of these observations and of similar reports in the literature, the author concludes that there are great individual differences in the sensitivity to atropine.

He further points out that the described sensitivity to small doses is in strong contrast to the great tolerance of patients with parkinsonism and postencephalitis, who are known to tolerate up to 40 mg. daily. To be sure, even in these patients sudden delirious attacks have been known to occur. Sudden cessation of the medication must be avoided in these patients because it may give rise to unpleasant vegetative symptoms (sweating, vomiting and so on). During the summer, special caution is necessary in the administration of atropine, because it inhibits sweat secretion and consequently impairs the heat regulation and thus may cause collapse.

## Zeitschrift für Kinderheilkunde, Berlin

**61:** 135-264 (Aug. 9) 1939. Partial Index

Problem of Exsiccosis in Intoxication of Nurslings. V. Uher.—p. 135
Acute Pancreatic Necrosis in Rupture of Stomach in Child Aged 3 Years. F. Gross.—p. 142.
Time of Appearance of Agglutinin Against Bordet Gengou Bacilli. W. Dienst.—p. 148.
*Endemic Varicella After Herpes Zoster During Childhood. W. Matheja. —p. 153.
Question of Increase in Resistance Following Prolonged Prophylactic Administration of Vitamin C. Margarete Peters.—p. 179.
Bacterial Growth in Raw and Cooked Breast Milk (Bactericidal Power of Human Milk). W. Goeters.—p. 184.
Treatment of Chorea Minor with Phenobarbital and Myoarsphenamine. Erika Supplieth.—p. 206.

**Endemic Varicella After Herpes Zoster.**—According to Matheja the question of a causal connection between herpes zoster and varicella is still undecided. Whereas some believe that the same virus causes these two disorders, others reject this theory. The author made observations which indicate the identity of the virus of varicella and that of herpes zoster. He reports the case of a child aged 3 years who was hospitalized on account of beginning whooping cough and suspected gonorrhea. After several weeks of hospitalization the typical symptoms of herpes zoster developed, and sixteen days later varicella developed in two children who were in the same cubicle with this child. Another source of infection could be definitely excluded because these children had been isolated for some time and no patients with varicella were in the clinic at this time or previously. A second case of herpes zoster was observed in a child aged 2 years. Sixteen days later varicella developed in two children who were in the same ward with this child. These observations recalled an earlier concurrence of herpes zoster and varicella, which at the time had remained unexplained. Herpes zoster developed in a child aged 2 with active tuberculosis, and two weeks later varicella developed in a child aged 14 months who was in the same ward. The author reviews some attempts that have been made to corroborate the epidemiologic observations on the relationship between herpes zoster and varicella by serologic, immunobiologic and pathologic anatomic studies.

## Sovetskiy Vrachebnyy Zhurnal, Leningrad

June 30, 1939 (No. 12) Pp. 625-672. Partial Index

*Rheumatic Cardiac Lesions in Children. V. O. Mochan.—p. 631.
Salicylate Therapy of Rheumatism. S. G. Artemiev.—p. 641.
Clinical and Experimental Study of Action of White Streptocid on Gonorrhea. P. P. Semenov.—p. 647.
Sacralization as Pathogenic Factor in Etiology of Lumbo-Ischiatic (Sciatic) Syndrome. A. A. Sergeev.—p. 653.

**Rheumatic Cardiac Lesions in Children.**—According to Mochan, recent microscopic and experimental studies have demonstrated that the duration of rheumatism in both adults and children extends over a longer period than was previously believed. The more dangerous sclerosing period culminating in valvular lesions takes place during the afebrile stage with the child in apparently good condition. It appeared therefore advisable to prolong the treatment so as to include the various phases of the rheumatic infection. A new system was instituted in 1894; it consisted of three units, the university hospital, the sanatorium and the dispensary. On leaving the hospital the patient is transferred immediately to the sanatorium, where he spends all of the sclerosing period, after which he is supervised by the dispensary. The sanatorium treatment includes various physical therapeutic, balneologic and training methods. Of the 900 cases treated by this method since March 1934, the author is able to report 663. The mortality rate in this group amounted to 4.4 per cent, 7.8 per cent for the boys and 1.7 per cent for the girls. Age appeared to be an important factor in the incidence of the disease, the greatest number occurring in children from 11 to 15 years of age. Not more than 5.6 per cent escaped any cardiac damage. Nine per cent of this small group were observed during the first attack, 3.9 per cent escaped any damage with the second and subsequent attacks and only 1.8 per cent in the group of ambulatory polyarthritic form. Acute carditis culminated in a valvular lesion in 61.5 per cent, while 38.5 per cent did not develop any valvular lesion. Acute endocarditis yielded 4.1 per cent of recoveries; 7.4 per cent of this group were observed with the first attack and only 1 per cent after recurring attacks. Myocarditis alone was observed in one third of the cases. It was present most frequently in the group having one attack only, less frequently with the second and recurring attacks, and least frequently in the ambulatory polyarthritic form. Pancarditis was observed four times as frequently after recurrent attacks as after one attack. The predominant valvular lesion was mitral and was present in one half of the cases after the first attack. About 60 per cent reach maturity with valvular lesions and in a hyperergic phase predisposing to recurring attacks. Analysis of measurements in 125 cases utilizing the statistical variation method suggests that there is no predisposing morphologic constitution. On the other hand, sexual maturity appears to be a predisposing factor.

## Geneeskundig Tijdschr. v. Nederl.-Indië, Batavia

**79:** 2097-2168 (Aug. 22) 1939. Partial Index

Echinostomiasis in Celebes Caused by Eating of Sweet Water Mussels. C. Bonne and J. H. Sandground.—p. 2116.
*Treatment of Venereal Lymphogranuloma with Combination of Sulfanilamide and Fuadin. J. J. Krijnen.—p. 2162.

**Sulfanilamide and Fuadin in Venereal Lymphogranuloma.**—Krijnen says that the combined administration of sulfanilamide and fuadin (sodium antimony biscatechol-disulfonate of sodium) was recommended by Gjuric for the treatment of venereal lymphogranuloma. Gjuric gave intramuscular injections of fuadin every other day, beginning with 3.5 cc. and later giving 5 cc.; he gave sulfanilamide five times daily (each time one tablet of 0.5 Gm.) for five days and then four times daily for three days. Whenever necessary, treatment with sulfanilamide was renewed after from three to five days. Krijnen, who used this combination therapy in twenty cases of venereal lymphogranuloma, slightly modified Gjuric's procedure by giving the first two or three injections of fuadin daily instead of every other day, and by lengthening the interval between the sulfanilamide series to at least a week. The total duration of the treatment in the author's cases varied between five and nineteen days, the average being eleven days. The number of fuadin injections was between three and ten and the number of sulfanilamide days between five and thirteen. Relapses occurred in four of the cases, but these recurrences all yielded to the same treatment in from five to seven days. The author gained the impression that the number of relapses was less when the treatment was prolonged.

## Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam

**83:** 4609-4712 (Sept. 23) 1939. Partial Index

Beginning Tuberculosis. H. R. Gerbrandy.—p. 4613.
Decurvon, a Pictin Insulin with Protracted Action. B. Brahn and M. T. Langner.—p. 4621.
Chronic Relapsing Sepsis Caused by Meningococci. G. F. van Balen. —p. 4632.
*Hemostatic Remedies as Prophylactics in Tonsillectomies. L. B. W. Jongkees.—p. 4640.
Treatment of Bronchial Asthma. C. L. de Jongh.—p. 4649.

**Hemostatic Remedies for Tonsillectomies.**—Jongkees says that many otorhinolaryngologists are in the habit of subjecting patients who are to undergo tonsillectomy to prolonged administration of calcium salts. They resort to this measure in the hope of reducing postoperative bleeding. Whether there exists theoretical justification for this treatment is still an unsolved problem. The author studied the effect of calcium salts in a group of children (from 4 to 12 years of age) who were to undergo tonsillectomy. He made these studies with the aid of a method which determines the coagulation and bleeding times fairly accurately and without elaborate instruments. He found that calcium salts, taken orally, shorten the coagulation time. However, to produce this effect it is not necessary to

give calcium salts for a long time, the effect being produced in a few hours. The author describes his observations on the effectiveness of a certain hemostatic preparation which he found ineffective in oral and only slightly effective in intramuscular injection. He also observed that the bleeding time is influenced neither by the oral nor by the intramuscular administration of calcium salts.

## Acta Obstet. et Gynec. Scandinavica, Stockholm

**19:** 247-370 (No. 3) 1939. Partial Index

Primary Ulcerous Pneumococcic Vaginitis. Gösta Leander.—p. 249.
Contribution to Diagnosis of Strangulating Endometriosis in Sigmoid Colon, with Reference to Case Observed. H. Josefsson.—p. 256.
Abdominal Pregnancy: Case in Which Mature, Living Fetus Was Obtained by Operation. E. Bergenfeldt.—p. 272.
Hyperemesis Gravidarum. E. Schjött-Rivers.—p. 290.
*Clinical Experience with Estilbin. S. Felding and E. Møller-Christensen. —p. 337.
Radial Paralysis in the Newborn. E. Hauch and M. Ottsen.—p. 345.
*Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn (Hypothrombinemia Haemorrhagica Neonatorum): Preliminary Report. K. K. Nygaard.—p. 361.

**Clinical Experience with Diethylstilbestrol.**—Felding and Møller-Christensen review reports on the biologic effect of diethylstilbestrol in rats and mice. It was observed that whereas 50 micrograms of diethylstilbestrol administered daily for ten days produced the characteristic aspects of uterine estrus in castrated rats, it was necessary to administer 100 micrograms of estrone for nineteen days to evoke the same reaction. However, on the mammae of castrated rats the effect of diethylstilbestrol proved to be only about one fifth that of estrone. On the hypophysis diethylstilbestrol had the same effect as estrone. They first give a tabulated report of the clinical histories of thirty patients with the symptoms which accompany the cessation of the ovarian function. The table gives the age of the patients, the dose, the frequency of the injections, the number of injections and the result of the treatment. As a rule a dose of 1 mg. was administered two or three times a week. In five cases the treatment was without result and in four it had to be abandoned after a few injections, as they caused nausea and vomiting. In the other twenty-five cases the result was clinically satisfactory. It was noted that as a rule the first signs of improvement appeared after the third or fourth injection. In a second table the authors present the histories of ten patients with uterine hypoplasia. In these cases the diethylstilbestrol was administered in the expectation that it might cause growth of the uterus. The size of the uterus was determined by vaginal exploration. In five cases no enlargement of the uterus could be demonstrated and in two of these the treatment had to be discontinued because diethylstilbestrol caused nausea and vomiting. In the other five cases the treatment was satisfactory, a distinct growth of the uterus being demonstrable. Since January the authors have treated fifteen other patients who had climacteric symptoms with injections of diethylstilbestrol. In all these cases the results were favorable, and nausea and vomiting was observed in none of them. The authors reach the conclusion that diethylstilbestrol may be regarded as on a par with estrone preparations. However, in about one sixth of the cases it caused nausea and vomiting, and in some instances these symptoms were so severe that treatment had to be suspended.

**Vitamin K in Hemorrhagic Disease of the Newborn.**—Nygaard reports sixty-six cases of hemorrhagic disease of the newborn which occurred among 9,748 newborn infants. The investigations were induced on the one hand by the observation of a physiologic transitory prolongation of the coagulation time of the blood during the first week of life and on the other hand by the fact that the coagulation time is prolonged in cases of hemorrhage and further by the fact that the hemorrhages of the newborn coincide with the period of transitory prolongation of the coagulation time. In view of recent observations that hemorrhages in cases of obstructive jaundice are preceded by a lowering of the prothrombin content of the blood, investigation was made whether the abnormal coagulation of the blood of the newborn could originate in a deficiency of prothrombin. If this was so it seemed reasonable to try the administration of vitamin K, which exerts an antihemorrhagic effect. For the determination of the prothrombin time the method of Quick was used. In order to determine the physiologic variation of prothrombin during the first week of life, studies were made on thirty-one normal newborn infants. These studies indicated that a normal prothrombin time is maintained during the first ten hours after delivery but that a definite reduction of the prothrombin content becomes apparent during the second half of the first day. This low level is maintained during the following five days. From the sixth day prothrombin returns to the level found at the time of birth. Studies on the prothrombin content of some of the newborn infants with hemorrhage disclosed that in the majority of cases the onset of hemorrhage coincides with the period of transitory physiologic hypothrombinemia. Hemorrhages of the newborn generally occur when the physiologic hypothrombinemia exceeds that which is normally present at that time of life. This condition has been termed hypothrombinemia haemorrhagica neonatorum. Experiments with vitamin K revealed that the development of transitory hypothrombinemia apparently can be successfully prevented by the administration of vitamin K right after delivery. This may lead to effective prophylaxis of hypothrombinemia haemorrhagica neonatorum. Vitamin K administered to three patients with this type of hemorrhage exhibited a therapeutic effect equaling that of blood transfusion.

## Acta Psychiatrica et Neurologica, Copenhagen

**14:** 395-647 (No. 3-4) 1939. Partial Index

Cerebral Vasomotor Regulation: Method for Determination of Cerebral Control of Peripheral Circulation in Man. S. Christiansen, M. Fog and T. Vanggaard.—p. 413.
Clinical and Histopathologic Studies on Infantile Spinal Muscular Atrophy. F. Karlström and G. Wohlfart.—p. 453.
Syringomyelia and Cervical Ribs in Heterozygotic Twins. K. H. Krabbe. —p. 489.
Cranial Deformity and Syringomyelia: Three Cases. L. Laursen. —p. 509.
Ependymal Cysts in Third Cerebral Ventricle with Sudden Fatal Course. H. Marcus.—p. 527.
*Late Impairment of Spinal Cord in Curvature of Spinal Column, Especially in Those of Type of Scheuermann's Juvenile Kyphosis. G. Wretblad.—p. 617.

**Scheuermann's Juvenile Kyphosis.**—Wretblad points out that curvatures of the vertebral column, even those that are comparatively severe and those that develop within a comparatively short time, rarely cause severe medullary symptoms. It has been assumed that impairments of the spinal cord are entirely absent in cases of this type. Wretblad was able to observe changes in the spinal cord also in juvenile kyphosis (Scheuermann's kyphosis). He gives detailed histories of six cases, in all of which youths were involved who had performed hard physical labor; that is, they belonged to a group in which Scheuermann's kyphosis is especially frequent. An aspect that is typical of this form of kyphosis is that the development of the vertebral deformity is hardly noticed by the patient. This characteristic was observed in the described cases. Regarding the development of the medullary symptoms the author says that the patients generally observe the symptoms first on one side. In one of the reported cases the symptoms were restricted to one side for a year but then, in the course of a month, they developed with equal severity on the other side. In two cases the first symptoms were sensations of numbness and cold, but otherwise the dominating symptoms were weakness and lack of steadiness in the legs. In some of the cases weakness of the bladder or constipation developed. Examination revealed in one of the cases a mild spastic paraparesis and in the other cases a severe one which prevented walking entirely or almost entirely, also a reduction in sensitivity, the upper limits of which correspond to the medullary segment of the vertex of the kyphosis. Myelography indicated that at the vertex of the kyphosis there existed an obstruction in the circulation of the spinal fluid, in that the dura was probably pressed against the spinal cord. Opening of the dura counteracted this obstruction. Laminectomy and leaving the dura open produced favorable results in three cases in which the medullary symptoms were of a comparatively recent date. In another case, in which the medullary symptoms had existed for several years, death followed a short time after the operation and the necropsy revealed that irreparable medullary changes, caused by the kyphosis, had developed previous to the operation. The author thinks that it cannot be doubted that the kyphosis is the cause of the medullary symptoms. He cites factors in support of this contention.